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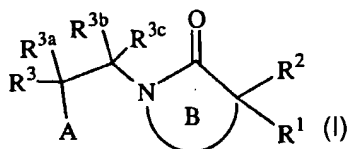
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(54) Title: NOVEL LACTAM METALLOPROTEASE INHIBITORS



(57) Abstract: The present application describes novel lactams and derivatives thereof of formula I: or pharmaceutically acceptable salt forms thereof, wherein ring B is a 4-8 membered cyclic amide comprising 0-3 additional heteroatoms selected from N, O, and S, which are useful as metalloprotease inhibitors.

## TITLE

## Novel Lactam Metalloprotease Inhibitors

## 5 FIELD OF THE INVENTION

This invention relates generally to novel lactam metalloprotease inhibitors, pharmaceutical compositions containing the same, and methods of using the same.

## 10 BACKGROUND OF THE INVENTION

There is now a body of evidence that metalloproteases (MP) are important in the uncontrolled breakdown of connective tissue, including proteoglycan and collagen, leading to resorption of the extracellular matrix. This is  
15 a feature of many pathological conditions, such as rheumatoid and osteoarthritis, corneal, epidermal or gastric ulceration; tumor metastasis or invasion; periodontal disease and bone disease. Normally these catabolic enzymes are tightly regulated at the level of their synthesis as  
20 well as at their level of extracellular activity through the action of specific inhibitors, such as alpha-2-macroglobulins and TIMP (tissue inhibitor of metalloprotease), which form inactive complexes with the MP's.

25 Osteo- and Rheumatoid Arthritis (OA and RA respectively) are destructive diseases of articular cartilage characterized by localized erosion of the cartilage surface. Findings have shown that articular cartilage from the femoral heads of patients with OA, for  
30 example, had a reduced incorporation of radiolabeled sulfate over controls, suggesting that there must be an enhanced rate of cartilage degradation in OA (Mankin et al. J. Bone Joint Surg. 52A, 1970, 424-434). There are four classes of

protein degradative enzymes in mammalian cells: serine, cysteine, aspartic and metalloproteases. The available evidence supports that it is the metalloproteases that are responsible for the degradation of the extracellular matrix of articular cartilage in OA and RA. Increased activities of collagenases and stromelysin have been found in OA cartilage and the activity correlates with severity of the lesion (Mankin et al. Arthritis Rheum. 21, 1978, 761-766, Woessner et al. Arthritis Rheum. 26, 1983, 63-68 and Ibid. 27, 1984, 305-312). In addition, aggrecanase has been identified that provides the specific cleavage product of proteoglycan, found in RA and OA patients (Lohmander L.S. et al. Arthritis Rheum. 36, 1993, 1214-22).

Therefore metalloproteinases (MP) have been implicated as the key enzymes in the destruction of mammalian cartilage and bone. It can be expected that the pathogenesis of such diseases can be modified in a beneficial manner by the administration of MP inhibitors, and many compounds have been suggested for this purpose (see Wahl et al. Ann. Rep. Med. Chem. 25, 175-184, AP, San Diego, 1990).

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is a cell-associated cytokine that is processed from a 26kd precursor form to a 17kd active form. TNF- $\alpha$  has been shown to be a primary mediator in humans and in animals, of inflammation, fever, and acute phase responses, similar to those observed during acute infection and shock. Excess TNF- $\alpha$  has been shown to be lethal. There is now considerable evidence that blocking the effects of TNF- $\alpha$  with specific antibodies can be beneficial in a variety of circumstances including autoimmune diseases such as rheumatoid arthritis (Feldman et al, Lancet, 1994, 344, 1105), non-insulin dependent diabetes melitus. (Lohmander L.S. et al. Arthritis Rheum. 36, 1993,

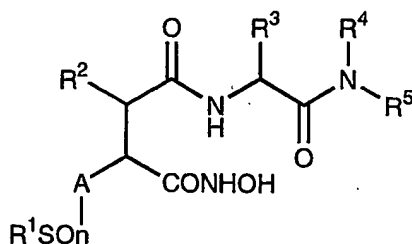
1214-22) and Crohn's disease (Macdonald T. et al. Clin. Exp. Immunol. 81, 1990, 301).

Compounds which inhibit the production of TNF- $\alpha$  are therefore of therapeutic importance for the treatment of inflammatory disorders. Recently it has been shown that a matrix metalloproteinase or family of metalloproteinases, hereafter known as TNF-convertases (TNF-C), as well as other MP's are capable of cleaving TNF from its inactive to active form (Gearing et al Nature, 1994, 370, 555). This invention describes molecules that inhibit this conversion and hence the secretion of active TNF- $\alpha$  from cells. These novel molecules provide a means of mechanism based therapeutic intervention for diseases including but not restricted to septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, Crohn's disease, inflammatory bowel diseases, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancer, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, osteo and rheumatoid arthritis, multiple sclerosis, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV and non-insulin dependent diabetes melitus.

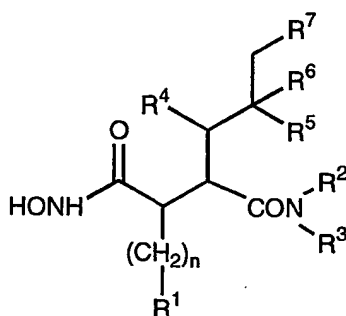
Since excessive TNF production has been noted in several disease conditions also characterized by MP-mediated tissue degradation, compounds which inhibit both MPs and TNF production may also have a particular advantage in diseases where both mechanisms are involved.

There are several patents that disclose hydroxamate and carboxylate based MP inhibitors.

W095/09841 describes compounds that are hydroxamic acid derivatives and are inhibitors of cytokine production.



European Patent Application Publication No. 574,758 A1,  
discloses hydroxamic acid derivatives as collagenase  
5 inhibitors having the general formula:



GB 2 268 934 A and WO 94/24140 claim hydroxamate inhibitors  
10 of MPs as inhibitors of TNF production.

The compounds of the current invention act as  
inhibitors of MPs, in particular aggrecanase and TNF. These  
novel molecules are provided as anti-inflammatory compounds  
and cartilage protecting therapeutics. The inhibition of  
15 aggrecanase, TNF-C, and other metalloproteinases by  
molecules of the present invention indicates they are anti-  
inflammatory and should prevent the degradation of cartilage  
by these enzymes, thereby alleviating the pathological  
conditions of osteo- and rheumatoid arthritis.

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#### SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to  
provide novel lactams that are useful as metalloprotease

inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

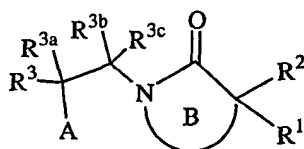
It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a method for treating inflammatory disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide novel lactams for use in therapy.

It is another object of the present invention to provide the use of novel lactams for the manufacture of a medicament for the treatment of an inflammatory disorder.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula I:

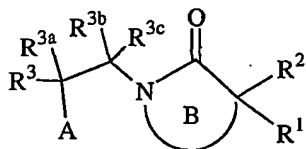


I

or pharmaceutically acceptable salt or prodrug forms thereof, wherein A, B, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3a</sup>, R<sup>3b</sup>, and R<sup>3c</sup> are defined below, are effective metalloprotease inhibitors.

## DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in an embodiment, the present invention provides a novel compound of formula I:



I

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

A is selected from  $\text{COR}^5$ ,  $-\text{CO}_2\text{H}$ ,  $\text{CH}_2\text{CO}_2\text{H}$ ,  $-\text{CO}_2\text{R}^6$ ,  $-\text{CONHOH}$ ,  $-\text{CH}_2\text{CONHOH}$ ,  $-\text{CONHOR}^5$ ,  $-\text{CONHOR}^6$ ,  $-\text{NHR}^a$ ,  $-\text{N}(\text{OH})\text{COR}^5$ ,  $-\text{SH}$ ,  $-\text{CH}_2\text{SH}$ ,  $-\text{SO}_2\text{NHR}^a$ ,  $\text{S}(=\text{NH})_2\text{R}^a$ ,  $\text{PO}(\text{OH})_2$ , and  $\text{PO}(\text{OH})\text{NHR}^a$ ;

ring B is a 4-8 membered cyclic amide containing from 0-3 additional heteroatoms selected from O,  $\text{NR}^a$ , and  $\text{S}(\text{O})_p$ , 0-1 additional carbonyl groups and 0-1 double bonds;

$\text{R}^1$  is  $\text{U-X-Y-Z-U}^a\text{-X}^a\text{-Y}^a\text{-Z}^a$ ;

U is absent or is selected from: O,  $\text{NR}^a$ ,  $\text{C}(\text{O})$ ,  $\text{C}(\text{O})\text{O}$ ,  $\text{OC}(\text{O})$ ,  $\text{C}(\text{O})\text{NR}^a$ ,  $\text{NR}^a\text{C}(\text{O})$ ,  $\text{OC}(\text{O})\text{O}$ ,  $\text{OC}(\text{O})\text{NR}^a$ ,  $\text{NR}^a\text{C}(\text{O})\text{O}$ ,  $\text{NR}^a\text{C}(\text{O})\text{NR}^a$ ,  $\text{S}(\text{O})_p$ ,  $\text{S}(\text{O})_p\text{NR}^a$ ,  $\text{NR}^a\text{S}(\text{O})_p$ , and  $\text{NR}^a\text{SO}_2\text{NR}^a$ ;

X is absent or selected from  $\text{C}_{1-10}$  alkylene,  $\text{C}_{2-10}$  alkenylene, and  $\text{C}_{2-10}$  alkynylene;

Y is absent or selected from O,  $\text{NR}^a$ ,  $\text{S}(\text{O})_p$ , and  $\text{C}(\text{O})$ ;

Z is absent or selected from a  $\text{C}_{3-13}$  carbocyclic residue substituted with 0-5  $\text{R}^b$  and a 5-14 membered heterocyclic system comprising carbon atoms and from

1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R<sup>b</sup>;

U<sup>a</sup> is absent or is selected from: O, NR<sup>a</sup>, C(O), C(O)O,  
 5 OC(O), C(O)NR<sup>a</sup>, NR<sup>a</sup>C(O), OC(O)O, OC(O)NR<sup>a</sup>, NR<sup>a</sup>C(O)O,  
 NR<sup>a</sup>C(O)NR<sup>a</sup>, S(O)<sub>p</sub>, S(O)<sub>p</sub>NR<sup>a</sup>, NR<sup>a</sup>S(O)<sub>p</sub>, and NR<sup>a</sup>SO<sub>2</sub>NR<sup>a</sup>;

X<sup>a</sup> is absent or selected from C<sub>1-10</sub> alkylene, C<sub>2-10</sub>  
 alkenylene, C<sub>2-10</sub> alkynylene;

10

Y<sup>a</sup> is absent or selected from O, NR<sup>a</sup>, S(O)<sub>p</sub>, and C(O);

Z<sup>a</sup> is selected from H, a C<sub>3-13</sub> carbocyclic residue  
 substituted with 0-5 R<sup>c</sup> and a 5-14 membered  
 15 heterocyclic system comprising carbon atoms and from  
 1-4 heteroatoms selected from the group consisting of  
 N, O, and S and substituted with 0-5 R<sup>c</sup>;

R<sup>2</sup> is selected from Q, C<sub>1-10</sub> alkylene-Q, C<sub>2-10</sub> alkenylene-Q,  
 20 C<sub>2-10</sub> alkynylene-Q, (CRR')<sub>r</sub>O(CRR')<sub>r</sub>-Q,  
 (CRR')<sub>r</sub>NR<sup>a</sup>(CRR')<sub>r</sub>-Q, (CRR')<sub>r</sub>NR<sup>a</sup>C(O)(CRR')<sub>r</sub>-Q,  
 (CRR')<sub>r</sub>C(O)NR<sup>a</sup>(CRR')<sub>r</sub>-Q, (CRR')<sub>r</sub>C(O)(CRR')<sub>r</sub>-Q,  
 (CRR')<sub>r</sub>C(O)O(CRR')<sub>r</sub>-Q, (CRR')<sub>r</sub>S(O)<sub>p</sub>(CRR')<sub>r</sub>-Q,  
 (CRR')<sub>r</sub>SO<sub>2</sub>NR<sup>a</sup>(CRR')<sub>r</sub>-Q, (CRR')<sub>r</sub>NR<sup>a</sup>C(O)NR<sup>a</sup>(CRR')<sub>r</sub>-Q,  
 25 (CRR')<sub>r</sub>OC(O)NR<sup>a</sup>(CRR')<sub>r</sub>-Q, and (CRR')<sub>r</sub>NR<sup>a</sup>C(O)O(CRR')<sub>r</sub>-Q;

R, at each occurrence, is independently selected from H,  
 CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CH=CH<sub>2</sub>, CH=CHCH<sub>3</sub>, and CH<sub>2</sub>CH=CH<sub>2</sub>;

30 R', at each occurrence, is independently selected from H,  
 CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, and CH(CH<sub>3</sub>)<sub>2</sub>;



alternatively,  $R^1$  and  $R^2$  combine to form a  $C_{3-13}$  carbocyclic residue substituted with  $R^{1'}$  and 0-3  $R^b$  or a 5-14 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with  $R^{1'}$  and 0-3  $R^b$ ;

Q is selected from H, a  $C_{3-13}$  carbocyclic residue substituted with 0-5  $R^b$  and a 5-14 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5  $R^b$ ;

15  $R^{1'}$  is  $U^a-X^a-Y^a-Z^a$ ;

$R^3$  is selected from H,  $C_{1-6}$  alkyl, and (3-10 membered carbocyclic or heterocyclic ring)(CRR')<sub>r</sub>-, wherein the 3-10 membered carbocyclic or heterocyclic ring comprises carbon atoms and 0-3 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;

25  $R^{3a}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;

$R^{3b}$  is selected from H,  $C_{1-6}$  alkyl, and (3-10 membered carbocyclic or heterocyclic ring)(CRR')<sub>r</sub>-, wherein the 3-10 membered carbocyclic or heterocyclic ring comprises carbon atoms and 0-3 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;

$R^{3c}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;

alternatively one of  $R^3$ ,  $R^{3a}$ ,  $R^{3b}$ , and  $R^{3c}$  maybe independently  
 5 selected from  $(CRR')_rOR^a$ ,  $(CRR')_rNR^aR^{a'}$ ,  $(CRR')_rC(O)R^a$ ,  
 $(CRR')_rC(O)OR^a$ ,  $(CRR')_rC(O)NR^aR^{a'}$ ,  $(CRR')_rS(O)_pR^a$ , and  
 $(CRR')_rS(O)_pNR^aR^{a'}$ , provided that in the group  
 $(CRR')_rS(O)_pR^a$ ,  $R^a$  is other than H;

10 alternatively,  $R^3$  and  $R^{3b}$  together with the carbon atoms to  
 which they are attached combine to form a 3-10 membered  
 carbocyclic or heterocyclic ring comprising carbon  
 atoms and 0-3 ring heteroatoms selected from O, N,  $NR^a$ ,  
 and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the  
 15 cyclic moiety contains other than an N-S, O-S, O-O, or  
 S-S bond;

alternatively,  $R^3$  and  $R^{3a}$  together with the carbon atom to  
 which they are attached combine to form a 3-10 membered  
 20 carbocyclic or heterocyclic ring comprising carbon  
 atoms and 0-2 ring heteroatoms selected from O, N,  $NR^a$ ,  
 and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the  
 cyclic moiety contains other than an N-S, O-S, O-O, or  
 S-S bond;

25 alternatively,  $R^{3b}$  and  $R^{3c}$  together with the carbon atom to  
 which they are attached combine to form a 3-10 membered  
 carbocyclic or heterocyclic ring comprising carbon  
 atoms and 0-2 ring heteroatoms selected from O, N,  $NR^a$ ,  
 30 and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the  
 cyclic moiety contains other than an N-S, O-S, O-O, or  
 S-S bond;

$R^a$ , at each occurrence, is independently selected from H,  
C<sub>1-4</sub> alkyl, phenyl and benzyl;

5  $R^{a'}$ , at each occurrence, is independently selected from H,  
C<sub>1-4</sub> alkyl, phenyl and benzyl;

$R^{a''}$ , at each occurrence, is independently selected from H,  
C<sub>1-4</sub> alkyl, benzyl, C<sub>3-7</sub> carbocyclic group, or a 5-6  
10 membered heteroaromatic ring containing 1-4 heteroatoms  
selected from the group consisting of N, O, and S;

alternatively,  $R^a$  and  $R^{a'}$  taken together with the nitrogen to  
which they are attached form a 5 or 6 membered ring  
comprising 0-1 additional heteroatoms selected from the  
15 group consisting of N, O, and S;

$R^b$ , at each occurrence, is independently selected from C<sub>1-6</sub>  
alkyl,  $OR^a$ , Cl, F, Br, I, =O, CN, NO<sub>2</sub>,  $NR^aR^{a'}$ ,  $C(O)R^{a''}$ ,  
C(O) $OR^a$ , C(O) $NR^aR^{a'}$ ,  $S(O)_2NR^aR^{a'}$ ,  $S(O)_pR^a$ , CF<sub>3</sub>, and  
20 CF<sub>2</sub>CF<sub>3</sub>;

$R^c$ , at each occurrence, is independently selected from C<sub>1-6</sub>  
alkyl,  $OR^a$ , Cl, F, Br, I, =O, CN, NO<sub>2</sub>,  $NR^aR^{a'}$ ,  $C(O)R^a$ ,  
C(O) $OR^a$ , C(O) $NR^aR^{a'}$ ,  $NR^aC(O)NR^aR^{a'}$ ,  $S(O)_2NR^aR^{a'}$ ,  $S(O)_pR^a$ ,  
25 CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, -CH(=NOH), -C(=NOH)CH<sub>3</sub>,  $(CRR')_sO(CRR')_sR^d$ ,  
 $(CRR')_sS(O)_p(CRR')_sR^d$ ,  $(CRR')_sNR^a(CRR')_sR^d$ , phenyl, and  
a 5-14 membered heterocyclic group comprising 1-4  
heteroatoms selected from the group consisting of N, O,  
and S;

30

$R^d$ , at each occurrence, is independently selected from  $C_{1-6}$  alkyl,  $OR^a$ , Cl, F, Br, I, =O, CN,  $NO_2$ ,  $NR^aR^{a'}$ ,  $C(O)R^a$ ,  $C(O)OR^a$ ,  $C(O)NR^aR^{a'}$ ,  $NR^aC(O)NR^aR^{a'}$ ,  $S(O)_2NR^aR^{a'}$ ,  $S(O)_pR^a$ ,  $CF_3$ ,  $CF_2CF_3$ , phenyl, and a 5-6 membered heterocyclic group comprising 1-4 heteroatoms selected from the group consisting of N, O, and S;

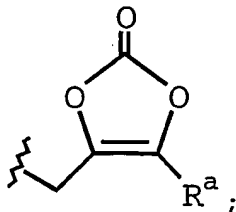
alternatively, when two  $R^d$ s are attached to adjacent atoms on  $R^3$ ,  $R^{3a}$ ,  $R^{3b}$ , or  $R^{3c}$ , they combine to form a 5-6 membered carbocyclic ring or a 5-6 membered heterocyclic ring comprising 1-4 heteroatoms selected from the group consisting of  $NR^a$ , O, and S;

$R^5$ , at each occurrence, is selected from  $C_{1-10}$  alkyl substituted with 0-2  $R^b$ , and  $C_{1-8}$  alkyl substituted with 0-2  $R^e$ ;

$R^e$ , at each occurrence, is independently selected from phenyl substituted with 0-3  $R^b$ , biphenyl substituted with 0-2  $R^b$ , naphthyl substituted with 0-3  $R^b$  and a 5-10 membered heteroaryl system comprising 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3  $R^b$ ;

$R^6$ , at each occurrence, is selected from phenyl, naphthyl,  $C_{1-10}$  alkyl-phenyl- $C_{1-6}$  alkyl-,  $C_{3-11}$  cycloalkyl,  $C_{1-6}$  alkylcarbonyloxy- $C_{1-3}$  alkyl-,  $C_{1-6}$  alkoxy carbonyloxy- $C_{1-3}$  alkyl-,  $C_{2-10}$  alkoxy carbonyl,  $C_{3-6}$  cycloalkylcarbonyloxy- $C_{1-3}$  alkyl-,  $C_{3-6}$  cycloalkoxy carbonyloxy- $C_{1-3}$  alkyl-,  $C_{3-6}$  cycloalkoxy carbonyl, phenoxycarbonyl, phenyloxy carbonyloxy- $C_{1-3}$  alkyl-, phenylcarbonyloxy- $C_{1-3}$

alkyl-, C<sub>1-6</sub> alkoxy-C<sub>1-6</sub> alkylcarbonyloxy-C<sub>1-3</sub> alkyl-,  
 [5-(C<sub>1-5</sub> alkyl)-1,3-dioxo-cyclopenten-2-one-yl)methyl,  
 (5-aryl-1,3-dioxo-cyclopenten-2-one-yl)methyl, -C<sub>1-10</sub>  
 alkyl-NR<sup>7</sup>R<sup>7a</sup>, -CH(R<sup>8</sup>)OC(=O)R<sup>9</sup>, -CH(R<sup>8</sup>)OC(=O)OR<sup>9</sup>, and



R<sup>7</sup> is selected from H and C<sub>1-10</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>3-6</sub>  
 cycloalkyl-C<sub>1-3</sub> alkyl-, and phenyl-C<sub>1-6</sub> alkyl-;

10 R<sup>7a</sup> is selected from H and C<sub>1-10</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>3-6</sub>  
 cycloalkyl-C<sub>1-3</sub> alkyl-, and phenyl-C<sub>1-6</sub> alkyl-;

R<sup>8</sup> is selected from H and C<sub>1-4</sub> linear alkyl;

15 R<sup>9</sup> is selected from H, C<sub>1-8</sub> alkyl substituted with 1-2 R<sup>e</sup>,  
 C<sub>3-8</sub> cycloalkyl substituted with 1-2 R<sup>e</sup>, and phenyl  
 substituted with 0-2 R<sup>b</sup>;

20 R<sup>e</sup>, at each occurrence, is selected from C<sub>1-4</sub> alkyl, C<sub>3-8</sub>  
 cycloalkyl, C<sub>1-5</sub> alkoxy, phenyl substituted with 0-2 R<sup>b</sup>;

p, at each occurrence, is selected from 0, 1, and 2;

25 r, at each occurrence, is selected from 0, 1, 2, 3, 4, and  
 5;

r', at each occurrence, is selected from 0, 1, 2, 3, 4, and  
 5;

s, at each occurrence, is selected from 0, 1, 2, and 3; and,

s', at each occurrence, is selected from 0, 1, 2, and 3.

5

[2] In a preferred embodiment, the present invention provides compounds, wherein:

10 A is selected from  $-\text{CO}_2\text{H}$ ,  $\text{CH}_2\text{CO}_2\text{H}$ ,  $-\text{CONHOH}$ ,  $-\text{CONHOR}^5$ ,  
 $-\text{CONHOR}^6$ ,  $-\text{N}(\text{OH})\text{COR}^5$ ,  $-\text{SH}$ , and  $-\text{CH}_2\text{SH}$ ;

ring B is a 4-6 membered cyclic amide containing from 0-3  
additional heteroatoms selected from O,  $\text{NR}^a$ , and  $\text{S}(\text{O})_p$ .  
15 0-1 additional carbonyl groups and 0-1 double bonds;

$\text{R}^1$  is  $\text{U-X-Y-Z-U}^a\text{-X}^a\text{-Y}^a\text{-Z}^a$ ;

U is absent or is selected from: O,  $\text{NR}^a$ ,  $\text{C}(\text{O})$ ,  $\text{C}(\text{O})\text{O}$ ,  
20  $\text{OC}(\text{O})$ ,  $\text{C}(\text{O})\text{NR}^a$ ,  $\text{NR}^a\text{C}(\text{O})$ ,  $\text{S}(\text{O})_p$ , and  $\text{S}(\text{O})_p\text{NR}^a$ ;

X is absent or selected from  $\text{C}_{1-6}$  alkylene,  $\text{C}_{2-6}$  alkenylene,  
and  $\text{C}_{2-6}$  alkynylene;

25 Y is absent or selected from O,  $\text{NR}^a$ , and  $\text{C}(\text{O})$ ;

Z is absent or selected from a  $\text{C}_{3-10}$  carbocyclic residue  
substituted with 0-5  $\text{R}^b$  and a 5-10 membered  
heterocyclic system comprising carbon atoms and from  
30 1-4 heteroatoms selected from the group consisting of  
N, O, and S and substituted with 0-5  $\text{R}^b$ ;

U<sup>a</sup> is absent or is selected from: O, NR<sup>a</sup>, C(O), C(O)O,  
OC(O), C(O)NR<sup>a</sup>, NR<sup>a</sup>C(O), S(O)<sub>p</sub>, and S(O)<sub>p</sub>NR<sup>a</sup>;

X<sup>a</sup> is absent or selected from C<sub>1-6</sub> alkylene, C<sub>2-6</sub> alkenylene,  
5 C<sub>2-6</sub> alkynylene;

Y<sup>a</sup> is absent or selected from O, NR<sup>a</sup>, and C(O);

Z<sup>a</sup> is selected from H, a C<sub>5-10</sub> carbocyclic residue  
10 substituted with 0-5 R<sup>c</sup> and a 5-10 membered  
heterocyclic system comprising carbon atoms and from  
1-4 heteroatoms selected from the group consisting of  
N, O, and S and substituted with 0-5 R<sup>c</sup>;

15 R<sup>2</sup> is selected from Q, C<sub>1-6</sub> alkylene-Q, C<sub>2-6</sub> alkenylene-Q,  
C<sub>2-6</sub> alkynylene-Q, (CRR')<sub>r</sub>O(CRR')<sub>r</sub>-Q,  
(CRR')<sub>r</sub>NR<sup>a</sup>(CRR')<sub>r</sub>-Q, (CRR')<sub>r</sub>NR<sup>a</sup>C(O)(CRR')<sub>r</sub>-Q,  
(CRR')<sub>r</sub>C(O)NR<sup>a</sup>(CRR')<sub>r</sub>-Q, (CRR')<sub>r</sub>C(O)(CRR')<sub>r</sub>-Q,  
(CRR')<sub>r</sub>C(O)O(CRR')<sub>r</sub>-Q, (CRR')<sub>r</sub>S(O)<sub>p</sub>(CRR')<sub>r</sub>-Q, and  
20 (CRR')<sub>r</sub>SO<sub>2</sub>NR<sup>a</sup>(CRR')<sub>r</sub>-Q;

R, at each occurrence, is independently selected from H,  
CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, and CH=CH<sub>2</sub>;

25 R', at each occurrence, is independently selected from H,  
CH<sub>3</sub>, and CH<sub>2</sub>CH<sub>3</sub>;

alternatively, R<sup>1</sup> and R<sup>2</sup> combine to form a C<sub>3-10</sub> carbocyclic  
residue substituted with R<sup>1'</sup> and 0-3 R<sup>b</sup> or a 5-10  
30 membered heterocyclic system comprising carbon atoms  
and from 1-4 heteroatoms selected from the group

consisting of N, O, and S and substituted with  $R^{1'}$  and 0-3  $R^b$ ;

5 Q is selected from H, a  $C_{5-10}$  carbocyclic residue substituted with 0-5  $R^b$  and a 5-10 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5  $R^b$ ;

10  $R^{1'}$  is  $U^a$ - $X^a$ - $Y^a$ - $Z^a$ ;

$R^3$  is selected from H,  $C_{1-6}$  alkyl, and (5-10 membered carbocyclic or heterocyclic ring)( $CRR'$ ) $_r$ -, wherein the 5-10 membered carbocyclic or heterocyclic ring  
15 comprises carbon atoms and 0-3 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;

20  $R^{3a}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;

$R^{3b}$  is selected from H,  $C_{1-6}$  alkyl, and (5-10 membered carbocyclic or heterocyclic ring)( $CRR'$ ) $_r$ -, wherein the 5-10 membered carbocyclic or heterocyclic ring  
25 comprises carbon atoms and 0-3 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;

30  $R^{3c}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;

alternatively one of  $R^3$ ,  $R^{3a}$ ,  $R^{3b}$ , and  $R^{3c}$  maybe independently selected from  $(CRR')_rOR^a$ ,  $(CRR')_rNR^aR^a$ ,  $(CRR')_rC(O)R^a$ ,



$(\text{CRR}')_r\text{C}(\text{O})\text{OR}^a$ ,  $(\text{CRR}')_r\text{C}(\text{O})\text{NR}^a\text{R}^a$ ,  $(\text{CRR}')_r\text{S}(\text{O})_p\text{R}^a$ , and  
 $(\text{CRR}')_r\text{S}(\text{O})_r\text{NR}^a\text{R}^a$ , provided that in the group  
 $(\text{CRR}')_r\text{S}(\text{O})_p\text{R}^a$ ,  $\text{R}^a$  is other than H;

5 alternatively,  $\text{R}^3$  and  $\text{R}^{3b}$  together with the carbon atoms to  
 which they are attached combine to form a 4-10 membered  
 carbocyclic or heterocyclic ring comprising carbon  
 atoms and 0-3 ring heteroatoms selected from O, N,  $\text{NR}^a$ ,  
 and  $\text{S}(\text{O})_p$  and substituted with 0-2  $\text{R}^d$ , provided that the  
 10 cyclic moiety contains other than an N-S, O-S, O-O, or  
 S-S bond;

alternatively,  $\text{R}^3$  and  $\text{R}^{3a}$  together with the carbon atom to  
 which they are attached combine to form a 4-10 membered  
 15 carbocyclic or heterocyclic ring comprising carbon  
 atoms and 0-2 ring heteroatoms selected from O, N,  $\text{NR}^a$ ,  
 and  $\text{S}(\text{O})_p$  and substituted with 0-2  $\text{R}^d$ , provided that the  
 cyclic moiety contains other than an N-S, O-S, O-O, or  
 S-S bond;

20 alternatively,  $\text{R}^{3b}$  and  $\text{R}^{3c}$  together with the carbon atom to  
 which they are attached combine to form a 4-10 membered  
 carbocyclic or heterocyclic ring comprising carbon  
 atoms and 0-2 ring heteroatoms selected from O, N,  $\text{NR}^a$ ,  
 25 and  $\text{S}(\text{O})_p$  and substituted with 0-2  $\text{R}^d$ , provided that the  
 cyclic moiety contains other than an N-S, O-S, O-O, or  
 S-S bond;

$\text{R}^b$ , at each occurrence, is independently selected from  $\text{C}_{1-6}$   
 30 alkyl,  $\text{OR}^a$ , Cl, F, Br, I, =O, CN,  $\text{NO}_2$ ,  $\text{NR}^a\text{R}^a$ ,  $\text{C}(\text{O})\text{R}^a$ ,  
 $\text{C}(\text{O})\text{OR}^a$ ,  $\text{C}(\text{O})\text{NR}^a\text{R}^a$ ,  $\text{S}(\text{O})_2\text{NR}^a\text{R}^a$ ,  $\text{S}(\text{O})_p\text{R}^a$ ,  $\text{CF}_3$ , and  
 $\text{CF}_2\text{CF}_3$ ;

$R^c$ , at each occurrence, is independently selected from  $C_{1-6}$  alkyl,  $OR^a$ , Cl, F, Br, I, =O, CN,  $NO_2$ ,  $NR^aR^{a'}$ ,  $C(O)R^a$ ,  $C(O)OR^a$ ,  $C(O)NR^aR^{a'}$ ,  $NR^aC(O)NR^aR^{a'}$ ,  $S(O)_2NR^aR^{a'}$ ,  $S(O)_pR^a$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $-CH(=NOH)$ ,  $-C(=NOH)CH_3$ ,  $(CRR')_sO(CRR')_sR^d$ ,  $(CRR')_sS(O)_p(CRR')_sR^d$ ,  $(CRR')_sNR^a(CRR')_sR^d$ , phenyl, and a 5-10 membered heterocyclic group comprising 1-4 heteroatoms selected from the group consisting of N, O, and S;

$R^d$ , at each occurrence, is independently selected from  $C_{1-6}$  alkyl,  $OR^a$ , Cl, F, Br, I, =O, CN,  $NO_2$ ,  $NR^aR^{a'}$ ,  $C(O)R^a$ ,  $C(O)OR^a$ ,  $C(O)NR^aR^{a'}$ ,  $NR^aC(O)NR^aR^{a'}$ ,  $S(O)_2NR^aR^{a'}$ ,  $S(O)_pR^a$ ,  $CF_3$ ,  $CF_2CF_3$ , phenyl, and a 5-6 membered heterocyclic group comprising 1-4 heteroatoms selected from the group consisting of N, O, and S;

alternatively, when two  $R^d$ s are attached to adjacent atoms on  $R^3$ ,  $R^{3a}$ ,  $R^{3b}$ , or  $R^{3c}$ , they combine to form a 5-6 membered carbocyclic ring or a 5-6 membered heterocyclic ring comprising 1-4 heteroatoms selected from the group consisting of  $NR^a$ , O, and S;

$r$ , at each occurrence, is selected from 0, 1, 2, 3, and 4;

$r'$ , at each occurrence, is selected from 0, 1, 2, 3, and 4;

$s$ , at each occurrence, is selected from 0, 1, and 2; and,

$s'$ , at each occurrence, is selected from 0, 1, and 2.

[3] In another preferred embodiment, the present invention provides compounds, wherein:

A is selected from  $-\text{CO}_2\text{H}$ ,  $\text{CH}_2\text{CO}_2\text{H}$ ,  $-\text{CONHOH}$ ,  $-\text{CONHOR}^5$ , and  
5  $-\text{N}(\text{OH})\text{COR}^5$ ;

ring B is a 5-6 membered cyclic amide containing from 0-2  
additional heteroatoms selected from O,  $\text{NR}^a$ , and  $\text{S}(\text{O})_p$ ,  
0-1 additional carbonyl groups and 0-1 double bonds;

10

$\text{R}^1$  is  $\text{U-X-Y-Z-U}^a\text{-X}^a\text{-Y}^a\text{-Z}^a$ ;

15

U is absent or is selected from: O,  $\text{NR}^a$ ,  $\text{C}(\text{O})$ ,  $\text{C}(\text{O})\text{NR}^a$ , and  
 $\text{S}(\text{O})_p$ ;

X is absent or is  $\text{C}_{1-4}$  alkylene;

Y is absent or selected from O and  $\text{NR}^a$ ;

20

Z is absent or selected from a  $\text{C}_{5-6}$  carbocyclic residue  
substituted with 0-3  $\text{R}^b$  and a 5-6 membered heterocyclic  
system comprising carbon atoms and from 1-4 heteroatoms  
selected from the group consisting of N, O, and S and  
substituted with 0-3  $\text{R}^b$ ;

25

$\text{U}^a$  is absent or is selected from: O,  $\text{NR}^a$ ,  $\text{C}(\text{O})$ ,  $\text{C}(\text{O})\text{NR}^a$ , and  
 $\text{S}(\text{O})_p$ ;

30

$\text{X}^a$  is absent or selected from  $\text{C}_{1-6}$  alkylene and  $\text{C}_{2-6}$   
alkenylene;

$\text{Y}^a$  is absent or selected from O and  $\text{NR}^a$ ;

$Z^a$  is selected from H, a C<sub>5-10</sub> carbocyclic residue substituted with 0-3 R<sup>c</sup> and a 5-10 membered heterocyclic system comprising carbon atoms and from  
5 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3 R<sup>c</sup>;

R<sup>2</sup> is selected from Q, C<sub>1-6</sub> alkylene-Q, C<sub>2-6</sub> alkenylene-Q, (CRR')<sub>r</sub>O(CRR')<sub>r</sub>-Q, (CRR')<sub>r</sub>NR<sup>a</sup>(CRR')<sub>r</sub>-Q, and  
10 (CRR')<sub>r</sub>C(O)(CRR')<sub>r</sub>-Q;

R, at each occurrence, is independently selected from H, CH<sub>3</sub>, and CH<sub>2</sub>CH<sub>3</sub>;

15 R', at each occurrence, is independently selected from H and CH<sub>3</sub>;

alternatively, R<sup>1</sup> and R<sup>2</sup> combine to form a C<sub>5-6</sub> carbocyclic residue substituted with R<sup>1'</sup> and 0-3 R<sup>b</sup> or a 5-6  
20 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with R<sup>1'</sup> and 0-3 R<sup>b</sup>;

25 Q is selected from H, a C<sub>5-6</sub> carbocyclic residue substituted with 0-5 R<sup>b</sup> and a 5-6 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R<sup>b</sup>;

30

R<sup>1'</sup> is U<sup>a</sup>-X<sup>a</sup>-Y<sup>a</sup>-Z<sup>a</sup>;

$R^3$  is selected from H,  $C_{1-6}$  alkyl, and (5-6 membered carbocyclic or heterocyclic ring)  $(CH_2)_r-$ , wherein the 5-6 membered carbocyclic or heterocyclic ring comprises carbon atoms and 0-2 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;

$R^{3a}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;

$R^{3b}$  is selected from H,  $C_{1-6}$  alkyl, and (5-6 membered carbocyclic or heterocyclic ring)  $(CH_2)_r-$ , wherein the 5-6 membered carbocyclic or heterocyclic ring comprises carbon atoms and 0-2 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an, N-S, O-S, O-O, or S-S bond;

$R^{3c}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;

alternatively one of  $R^3$ ,  $R^{3a}$ ,  $R^{3b}$ , and  $R^{3c}$  is independently selected from  $(CRR')_rOR^a$ ,  $(CRR')_rNR^aR^{a'}$ ,  $(CRR')_rC(O)R^a$ ,  $(CRR')_rC(O)OR^a$ ,  $(CRR')_rC(O)NR^aR^{a'}$ ,  $(CRR')_rS(O)_pR^a$ , and  $(CRR')_rS(O)_pNR^aR^{a'}$ , provided that in the group  $(CRR')_rS(O)_pR^a$ ,  $R^a$  is other than H;

alternatively,  $R^3$  and  $R^{3b}$  together with the carbon atoms to which they are attached combine to form a 4-8 membered carbocyclic or heterocyclic ring comprising carbon atoms and 0-2 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;

- alternatively,  $R^3$  and  $R^{3a}$  together with the carbon atom to which they are attached combine to form a 5-8 membered carbocyclic or heterocyclic ring comprising carbon atoms and 0-2 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;
- alternatively,  $R^{3b}$  and  $R^{3c}$  together with the carbon atom to which they are attached combine to form a 5-8 membered carbocyclic or heterocyclic ring comprising carbon atoms and 0-2 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;

$R^c$ , at each occurrence, is independently selected from  $C_{1-6}$  alkyl,  $OR^a$ , Cl, F, Br, I, =O, CN,  $NO_2$ ,  $NR^aR^a'$ ,  $C(O)R^a$ ,  $C(O)OR^a$ ,  $C(O)NR^aR^a'$ ,  $NR^aC(O)NR^aR^a'$ ,  $S(O)_2NR^aR^a'$ ,  $S(O)_pR^a$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $-CH(=NOH)$ ,  $-C(=NOH)CH_3$ , and phenyl;

$r$ , at each occurrence, is selected from 0, 1, 2, and 3; and,

$r'$ , at each occurrence, is selected from 0, 1, 2, and 3.

[4] In another preferred embodiment, the present invention provides compounds, wherein:

30

A is selected from  $-CO_2H$ ,  $CH_2CO_2H$ ,  $-CONHOH$ ,  $-CONHOR^5$ , and  $-N(OH)COR^5$ ;

- ring B is a 5 membered cyclic amide containing from 0-1 additional heteroatoms selected from O, NR<sup>a</sup>, and S(O)<sub>p</sub>, 0-1 additional carbonyl groups and 0-1 double bonds;
- 5 R<sup>1</sup> is U-X-Y-Z-U<sup>a</sup>-X<sup>a</sup>-Y<sup>a</sup>-Z<sup>a</sup>;
- U is absent;
- X is absent;
- 10 Y is absent;
- Z is absent or selected from phenyl substituted with 0-2 R<sup>b</sup> and a 5-6 membered heteroaryl comprising carbon atoms and from 1-4 heteroatoms selected from the group
- 15 consisting of N, O, and S and substituted with 0-3 R<sup>b</sup>;
- U<sup>a</sup> is absent or is O;
- 20 X<sup>a</sup> is absent or selected from C<sub>1-4</sub> alkylene and C<sub>2-4</sub> alkenylene;
- Y<sup>a</sup> is absent or is O;
- 25 Z<sup>a</sup> is selected from H, a C<sub>6-10</sub> aryl residue substituted with 0-3 R<sup>c</sup> and a 5-10 membered heteroaryl comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3 R<sup>c</sup>;
- 30 R<sup>2</sup> is selected from C<sub>1-6</sub> alkylene, (CRR')<sub>r</sub>OH, and (CRR')<sub>r</sub>NR<sup>a</sup>H;

$R^3$  is selected from H,  $C_{1-6}$  alkyl, and (5-6 membered carbocyclic or heterocyclic ring)  $(CH_2)_r-$ , wherein the 5-6 membered carbocyclic or heterocyclic ring comprises carbon atoms and 0-1 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ ;

$R^{3a}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;

$R^{3b}$  is selected from H,  $C_{1-6}$  alkyl, and (5-6 membered carbocyclic or heterocyclic ring)  $(CH_2)_r-$  wherein the 5-6 membered carbocyclic or heterocyclic ring comprises carbon atoms and 0-1 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ ;

$R^{3c}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;

alternatively,  $R^3$  and  $R^{3b}$  together with the carbon atoms to which they are attached combine to form a 4, 5, 6, 7 or 8 membered carbocyclic or heterocyclic ring comprising carbon atoms and 0-1 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ ;

alternatively,  $R^3$  and  $R^{3a}$  together with the carbon atom to which they are attached combine to form a 5-6 membered carbocyclic or heterocyclic ring comprising carbon atoms and 0-1 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ ;

alternatively,  $R^{3b}$  and  $R^{3c}$  together with the carbon atom to which they are attached combine to form a 5-6 membered carbocyclic or heterocyclic ring comprising carbon atoms and 0-1 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ ;



R<sup>c</sup>, at each occurrence, is independently selected from C<sub>1-6</sub> alkyl, OR<sup>a</sup>, Cl, F, Br, I, =O, CN, NO<sub>2</sub>, NR<sup>a</sup>R<sup>a'</sup>, C(O)R<sup>a</sup>, C(O)OR<sup>a</sup>, C(O)NR<sup>a</sup>R<sup>a'</sup>, S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a'</sup>, S(O)<sub>p</sub>R<sup>a</sup>, CF<sub>3</sub>, and phenyl;

r, at each occurrence, is selected from 0, 1, and 2; and,

r', at each occurrence, is selected from 0, 1, and 2.

[5] In another preferred embodiment, the present invention provides compounds, wherein:

15 (1*S*-*cis*)-2-[3-amino-3-[4-[2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxycyclohexanecarboxamide bis(trifluoroacetate) (salt);

20 (1*R*-*trans*)-2-[3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxycyclohexanecarboxamide bis(trifluoroacetate) (salt);

25 (1*R*-*trans*)-2-[3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]cyclohexanecarboxylic acid bis(trifluoroacetate) (salt);

30 (1*S*-*cis*)-2-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]cyclopentanecarboxylic acid bis(trifluoroacetate) (salt);

- (1*S*-*cis*)-2-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxycyclopentanecarboxamide bis(trifluoroacetate) (salt);
- (1*R*-*trans*)-2-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxycyclopentanecarboxamide bis(trifluoroacetate) (salt);
- (1*S*-*cis*)-2-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxy-4,4-dimethylcyclopentanecarboxamide bis(trifluoroacetate) (salt);
- (1*S*-*cis*)-1-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-2,3-dihydro-*N*-hydroxy-1*H*-indene-2-carboxamide bis(trifluoroacetate) (salt);
- (3*R*-*trans*)-4-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]tetrahydro-*N*-hydroxy-3-furancarboxamide bis(trifluoroacetate) (salt);
- ( $\beta$ *R*)-3-amino-*N*-hydroxy- $\beta$ -(2-methylpropyl)-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinepropanamide bis(trifluoroacetate) (salt);
- ( $\beta$ *R*)-3-amino- $\beta$ -(2-methylpropyl)-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinepropanoic acid bis(trifluoroacetate) (salt); and,

3-amino-*N*-hydroxy- $\alpha$ ,  $\alpha$ -dimethyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinepropanamide bis(trifluoroacetate) (salt);

5

or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel pharmaceutical composition, comprising: a  
10 pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a  
15 novel method for treating an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt form thereof.

20 In another embodiment, the present invention provides a novel method of treating a condition or disease mediated by MPs, TNF, aggrecanase, or a combination thereof in a mammal, comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound  
25 of formula I or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method of treating a condition or disease wherein the  
30 disease or condition is referred to as acute infection, acute phase response, age related macular degeneration, alcoholism, anorexia, asthma, autoimmune disease, autoimmune hepatitis, Bechet's disease, cachexia, calcium pyrophosphate

dihydrate deposition disease, cardiovascular effects, chronic fatigue syndrome, chronic obstruction pulmonary disease, coagulation, congestive heart failure, corneal ulceration, Crohn's disease, enteropathic arthropathy, Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease, gingivitis, glucocorticoid withdrawal syndrome, gout, graft versus host disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious arthritis, inflammation, intermittent hydrarthrosis, Lyme disease, meningitis, multiple sclerosis, myasthenia gravis, mycobacterial infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory disease, periodontitis, polymyositis/dermatomyositis, post-ischaemic reperfusion injury, post-radiation asthenia, psoriasis, psoriatic arthritis, pyoderma gangrenosum, relapsing polychondritis, Reiter's syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock, Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and tumor invasion by secondary metastases, spondylitis, stroke, systemic lupus erythematosus, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis.

In another embodiment, the present invention provides novel lactams for use in therapy.

In another embodiment, the present invention provides the use of novel lactams for the manufacture of a medicament for the treatment of an inflammatory disorder.

30

#### DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an

asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. When a ring system (e.g., carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbonyl group or double bond be part (i.e., within) of the ring.

When any variable (e.g.,  $R^b$ ) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2  $R^6$ , then said group may optionally be substituted with up to two  $R^6$  groups and  $R^6$  at each occurrence is selected independently from the definition of  $R^6$ . Also, combinations of substituents and/or variables are

permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. C<sub>1-10</sub> alkyl (or alkylene), is intended to include C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>9</sub>, and C<sub>10</sub> alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example -C<sub>v</sub>F<sub>w</sub> where v = 1 to 3 and w = 1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C<sub>1-10</sub> alkoxy, is intended to include C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>9</sub>, and C<sub>10</sub> alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl,

cyclobutyl, or cyclopentyl. C<sub>3-7</sub> cycloalkyl, is intended to include C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, and C<sub>7</sub> cycloalkyl groups. "Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more  
5 unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl. C<sub>2-10</sub> alkenyl (or alkenylene), is intended to include C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>9</sub>, and C<sub>10</sub> alkenyl groups. "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of  
10 either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl. C<sub>2-10</sub> alkynyl (or alkynylene), is intended to include C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>9</sub>, and C<sub>10</sub> alkynyl groups.

15 "Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like.

20 As used herein, "carbocycle" or "carbocyclic group" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of  
25 such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl,  
30 adamantyl, and tetrahydronaphthyl.

As used herein, the term "heterocycle" or "heterocyclic group" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic

heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, NH, O and S and including  
5 any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable  
10 structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that the heterocycle contains other than an N-O, N-S, O-S, O-O, or S-S  
15 bond. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic  
20 group" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, NH, O and S. It is to be  
25 noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl,  
30 benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-



dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indoliziny, indolyl, 3*H*-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinoliziny, quinoxaliny, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1*H*-indazolyl, oxazolidinyl, benztriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The term "amino acid" as used herein means an organic compound containing both a basic amino group and an acidic

carboxyl group. Included within this term are natural amino acids (e.g., L-amino acids), modified and unusual amino acids (e.g., D-amino acids), as well as amino acids which are known to occur biologically in free or combined form but usually do not occur in proteins. Included within this term are modified and unusual amino acids, such as those disclosed in, for example, Roberts and Vellaccio (1983) The Peptides, 5: 342-429, the teaching of which is hereby incorporated by reference. Natural protein occurring amino acids include, but are not limited to, alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, serine, threonine, tyrosine, tyrosine, tryptophan, proline, and valine. Natural non-protein amino acids include, but are not limited to arginosuccinic acid, citrulline, cysteine sulfinic acid, 3,4-dihydroxyphenylalanine, homocysteine, homoserine, ornithine, 3-moniodotyrosine, 3,5-diiodotryosine, 3,5,5'-triiodothyronine, and 3,3',5,5'-tetraiodothyronine. Modified or unusual amino acids which can be used to practice the invention include, but are not limited to, D-amino acids, hydroxylysine, 4-hydroxyproline, an N-Cbz-protected amino acid, 2,4-diaminobutyric acid, homoarginine, norleucine, N-methylaminobutyric acid, naphthylalanine, phenylglycine,  $\beta$ -phenylproline, tert-leucine, 4-aminocyclohexylalanine, N-methyl-norleucine, 3,4-dehydroproline, N,N-dimethylaminoglycine, N-methylaminoglycine, 4-aminopiperidine-4-carboxylic acid, 6-aminocaproic acid, trans-4-(aminomethyl)-cyclohexanecarboxylic acid, 2-, 3-, and 4-(aminomethyl)-benzoic acid, 1-aminocyclopentanecarboxylic acid, 1-aminocyclopropanecarboxylic acid, and 2-benzyl-5-aminopentanoic acid.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the  
5 tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the  
10 parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic  
15 salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional  
20 non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic,  
25 maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic.

The pharmaceutically acceptable salts of the present  
30 invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a

stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists  
5 of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable  
10 qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc...) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same  
15 and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the present invention are prepared by  
20 modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group  
25 that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of  
30 alcohol and amine functional groups in the compounds of the present invention.

As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a

human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting its development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

#### SYNTHESIS

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup

procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

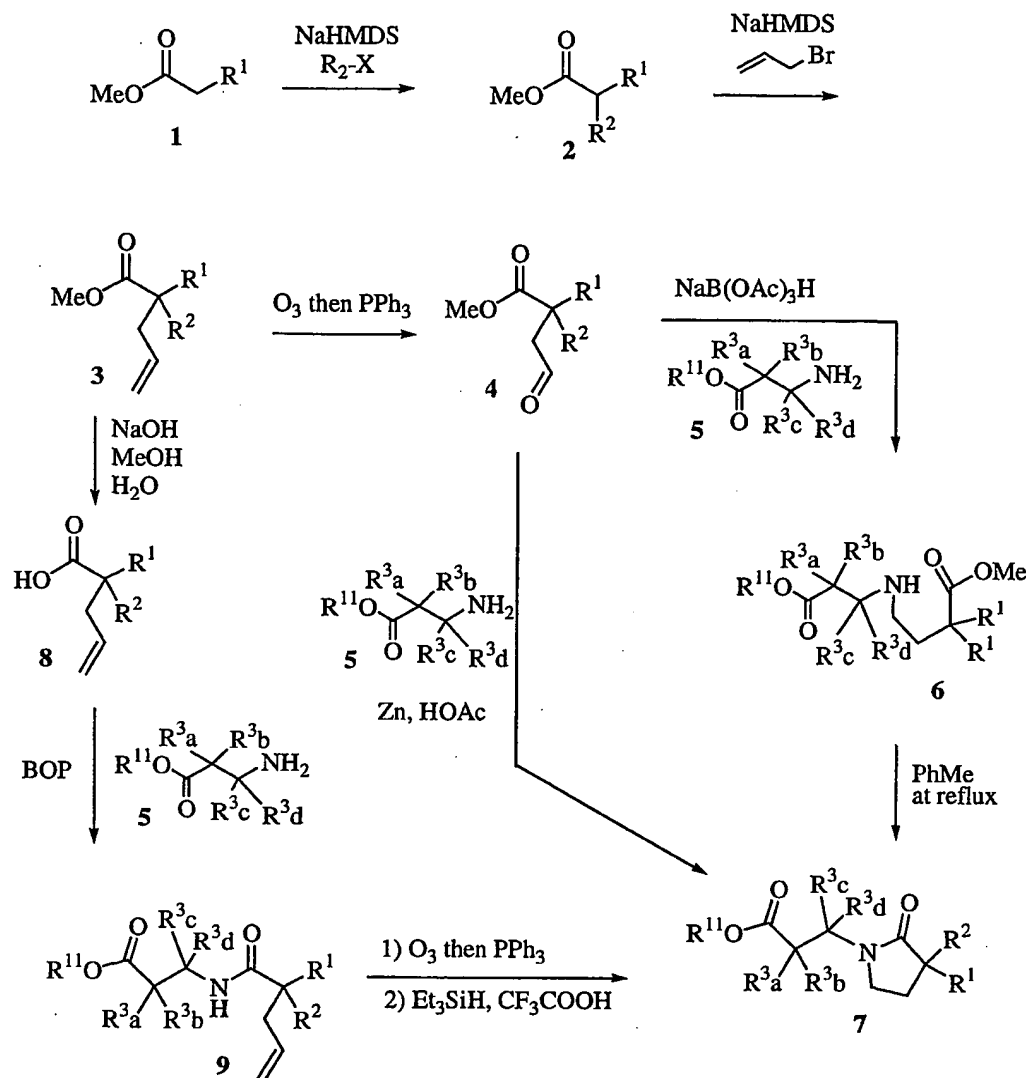
10       A series of  $\gamma$ -lactams of formula 10 are prepared by the methods outlined in Schemes 1 and 2.  $R^1$ -substituted methyl acetate 1 is deprotonated to form the enolate using bases such as sodium bis(trimethylsilyl)amide, lithium N,N-diisopropylamide, and sodium hydride. Alkylation with  $R^2$ -X provides 2. Further alkylation with allyl bromide under similar basic conditions gives ester 3. The olefin in 3 is then cleaved by ozonolysis or by dihydroxylation ( $OsO_4/NMO$ ) followed by diol cleavage ( $NaIO_4$ ) to give aldehyde 4. Treatment of the aldehyde 4 and the appropriately substituted  $\beta$ -amino acid 5 with zinc in acetic acid at elevated temperature leads to reductive amination and lactamization to give  $\gamma$ -lactam 7. The  $\gamma$ -lactamization gives a mixture of two diastereomers epimeric at the quaternary center. The diastereomers of 7 are either separated or taken to the next step as a mixture.

20       Alternatively, aldehyde 4 is converted to lactam 7 through a stepwise sequence. Condensation of 4 with the  $\beta$ -amino ester 5 through reductive amination provides secondary amine 6. The reductive amination can be affected with reagents such as sodium borohydride, sodium cyanoborohydride, and sodium triacetoxyborohydride. Amine 6 is converted to 7 via thermally induced lactamization or

methyl ester hydrolysis followed by amide bond formation using reagents such as BOP.

Lactam 7 can also be prepared from ester 3 through the carboxylic acid 8. Acid 8 and  $\beta$ -amino ester 5 can be  
5 coupled using standard peptide coupling reagents well known in the literature such as DCC, BOP, and TBTU (Bodanszky, M. in Peptide Chemistry A Practical Textbook, 2nd ed. Springer-Verlag, New York, 1993). Olefin degradation ( $O_3/PPh_3$ , or  $OsO_4/NaIO_4$ ) and deoxygenation ( $Et_3SiH/CF_3COOH$ ) gives lactam  
10 7.

Scheme 1



Many of the β-amino acid derivatives 5 are commercially available or are prepared from the commercial material by simple protecting group manipulations. Alternatively the β-amino acids can be prepared by a variety of methods discussed in "Enantioselective Synthesis of β-Amino Acids" edited by Eusebio Juraisti, Wiley-VCH publisher. Others are synthesized by methods outlined in Scheme Ia. The cyano acetate compound 301 may be reacted with reagents such as LDA to generate the enolate which may be alkylated with an electrophile such as an alkyl halide or tosylate to give



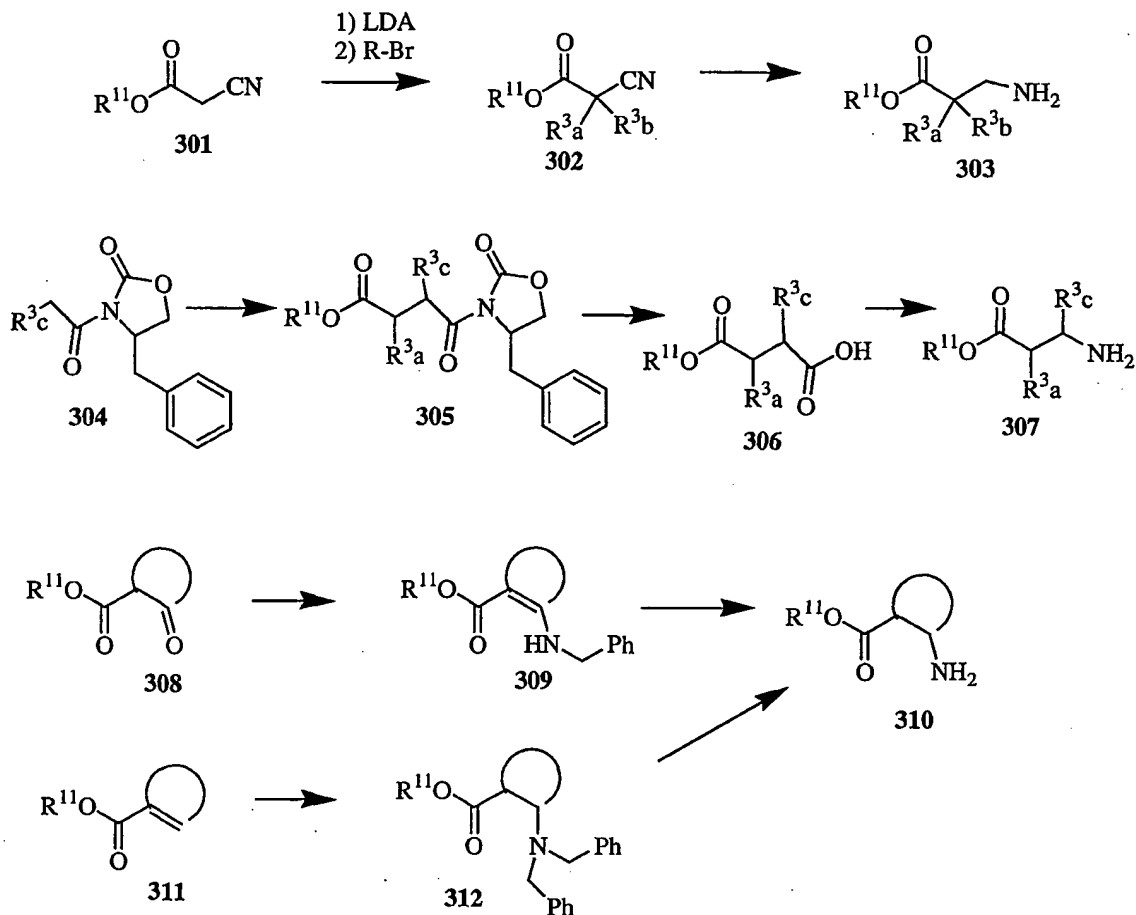
intermediate **302**. The nitrile can be reduced with reagents such as LAH or Raney nickel or hydrogenation over PtO<sub>2</sub> to give the  $\beta$ -amino acid **303**.

Alternatively the  $\beta$ -amino acid like compound **307** can be prepared starting with a protected ester like Evans oxazolidinone. Generating the enolate with bases like LDA and reacting this with a bromoacetate to give compounds like **305**. Hydrolysis of the oxazolidinone will give the carboxylic acid **306** and this can be transformed into the amine by a Curtius like reaction.

$\beta$ -amino acids can also be prepared from the starting ketoester compound **308**, reacting this with an amine like benzyl amine to prepare the enamine **309**. The enamine can be reduced by a number of methods like hydrogenation over Pd/C or stepwise with sodium triacetoxyborohydride to give the saturated intermediate and then hydrogenation with Pd/C to prepare compounds like **310**. Alternatively, the  $\beta$ -amino acid **310** can be prepared by reacting the  $\alpha$ - $\beta$  unsaturated ester in a Michael like fashion with an amine like benzyl amine or azide to give the amine compound **312**. The compound **312** can be reduced by hydrogenation conditions well known in the literature to give compound **310**.

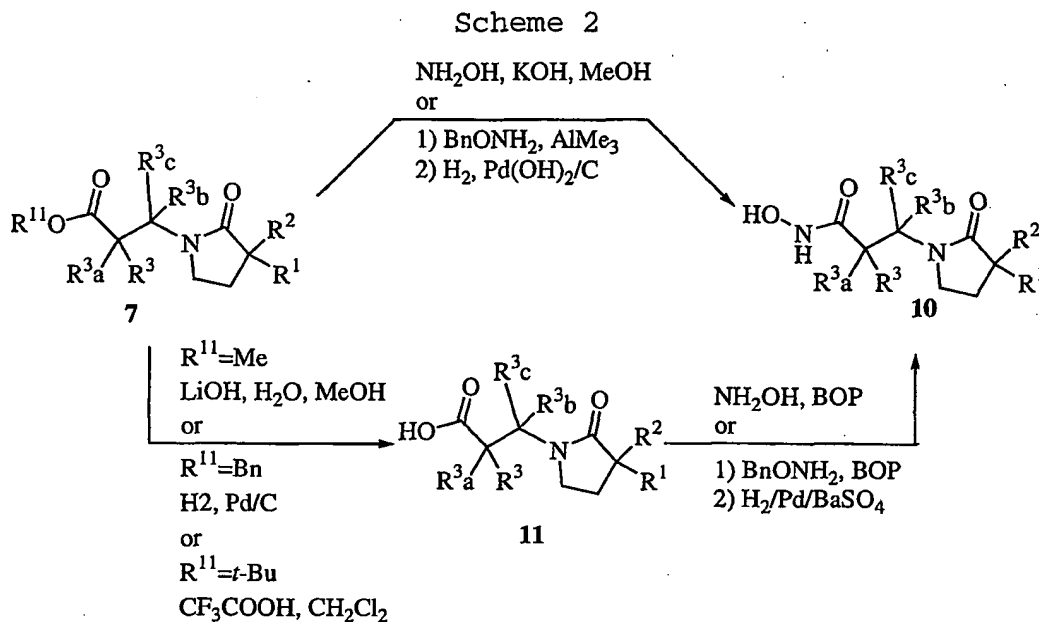
These reactions can be carried out in such a way as to prepare enantiospecific  $\beta$ -amino acids (G. Bartoli, C. Cimarilli, E. Marcantoni, G. Palmieri, M. Petrini, *J. Org. Chem.* **1994**, *59*, 5328-5335 and C. Cimerilli, G. Palmieri, *J. Org. Chem.* **1996**, *61*, 5557-5563.) or the isomers may be separated by chiral column HPLC.

Scheme Ia



- 5        The methyl ester of **7** ( $R^{11}=\text{Me}$ ) is converted to  
 hydroxamic acid **10** by treatment with hydroxylamine under  
 basic conditions (KOH or NaOMe) in methanol (Scheme 2). The  
 methyl ester **7** ( $R^{11}=\text{Me}$ ) can also be converted to benzyl  
 protected hydroxamic acid with O-benzylhydroxylamine using  
 10 Weinreb's trimethylalluminum conditions (Levin, J. I.;  
 Turos, E.; Weinreb, S. M. *Syn. Commun.* **1982**, 12, 989) or  
 Roskamp's bis[bis(trimethylsilyl)amido]tin reagent (Wang,  
 W.-B.; Roskamp, E. J. *J. Org. Chem.* **1992**, 57, 6101).  
 Hydrogenolysis then provides the hydroxamic acid **10**.  
 15 Alternatively, **10** can be prepared through the carboxylic  
 intermediate **11**. Carboxylic acid **11** is converted to **10** via

coupling with hydroxylamine or NH<sub>2</sub>OBn followed by deprotection.



5

A variety of ethers of 4-hydroxyphenyllactam **13** are prepared using intermediate **7** when  $\text{R}^1$  is benzyloxyphe-  
nyl group (Scheme 3). Removal of benzyl protecting group  
followed by alkylation with  $\text{R}^4\text{-X}$  produces **13**. The alkylation  
can be affected with bases such as  $\text{K}_2\text{CO}_3$ ,  $\text{Cs}_2\text{CO}_3$ ,  $\text{NaH}$ , and  $t\text{-BuOK}$ . Alternatively compounds like **13** can also be prepared  
with  $\text{R}^4\text{OH}$  under Mitsunobu conditions.

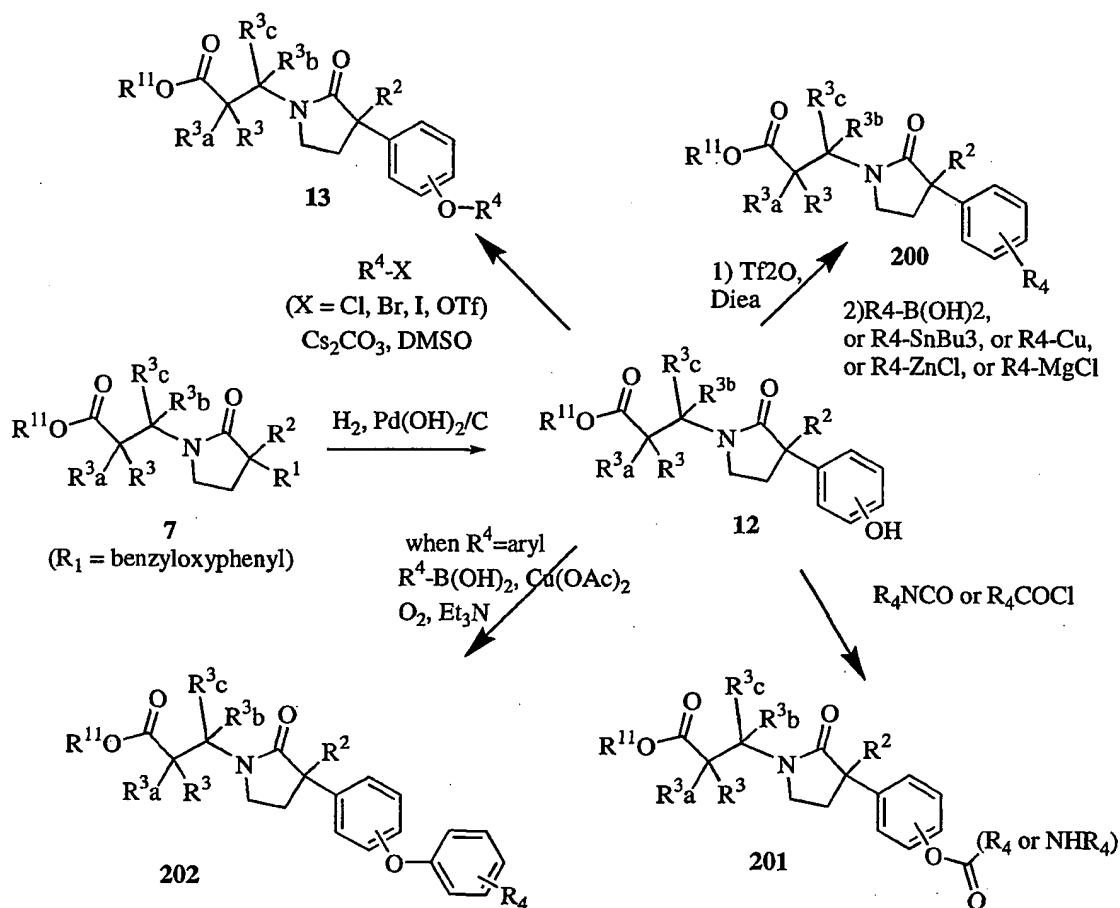
$\text{R}^4$  can be appended to the aromatic ring of compound  
**12** by converting the phenol to the aryl triflate with  
methods like triflic anhydride and DIEA in an appropriate  
solvent. The aryl triflate is reacted with an  
organometallic under Stille or Suzuki conditions in the  
presence of palladium(0) catalyst to give compound **200**.  
Alternatively, compound **12** reacts with lower or higher-order  
cuprates to give compound **200** as well.

Compounds like **201** can be prepared by reacting the  
phenol compound **12** with acyl halides or isocyanates in  
appropriate solvents and temperatures. The biaryl ethers

compound **202** can be prepared by treating compound **12** with aryl boronic acids in the presence of a copper catalyst.

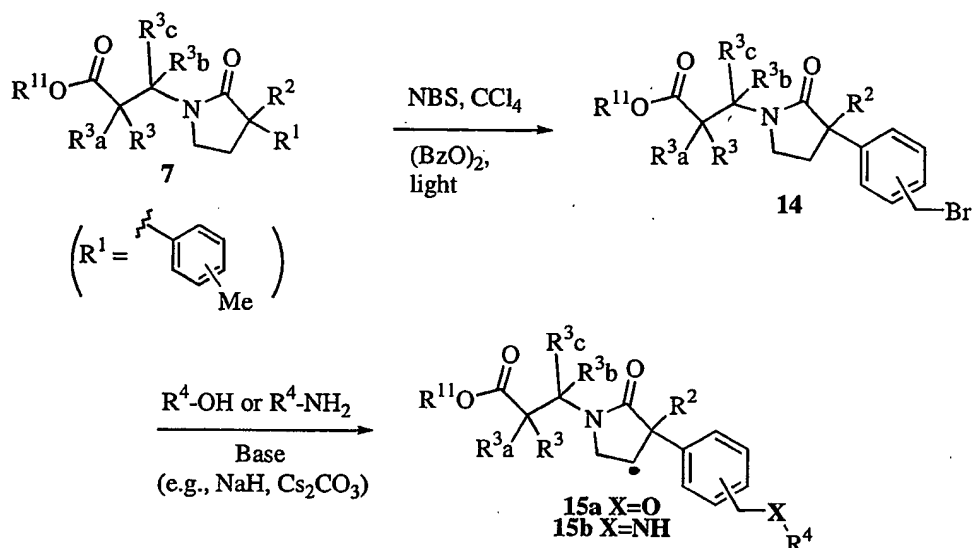
Compounds of Scheme 3 can be converted to their corresponding hydroxamic acids following the methods outlined in Scheme 2.

Scheme 3



Another series of phenyllactams of formula **15** is prepared following the sequence outlined in Scheme 4. Starting from **7** when  $R^1$  is phenyl methyl group, radical bromination with N-bromosuccinimide gives bromide **14**. Alkylation of **14** with  $R^4-OH$  or  $R^4-NH_2$  under basic conditions gives **15a** and **15b** respectively. Ester **15** is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

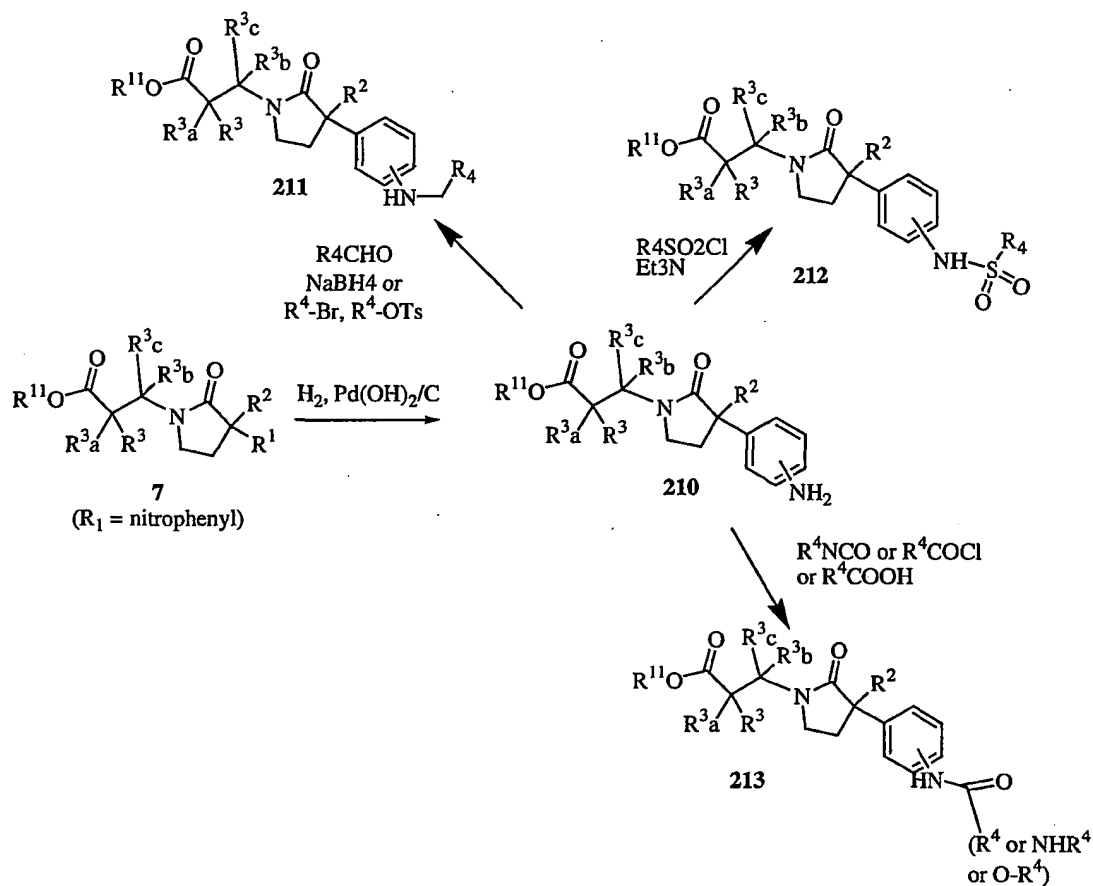
Scheme 4



Another series of phenyl lactams of Formula 10 like  
 5 those described in Scheme 5 can be prepared from compound **7**  
 where R<sup>1</sup> is nitrophenyl. The nitro group can be reduced to  
 the aniline compound **210** by methods well known in the  
 literature. The amine compound **211** can be prepared by  
 reaction of compound **210** with an appropriately substituted  
 10 aldehyde to give the imine that can be reduced by reagents  
 such as sodium borohydride or sodium triacetoxyborohydride.  
 Alternatively, the aniline compound **210** can be reacted with  
 an appropriately substituted compound containing a leaving  
 group like bromide or tosylate to give amine compound **211**.  
 15 The sulfonamide compound **212** can be prepared by  
 reaction of the aniline **210** with a substituted  
 sulfonylchloride by methods well known in the literature.  
 The amide compound **213** can be prepared by reacting the  
 aniline **210** with an acid chloride or carboxylic acid with a  
 20 coupling reagent used to make amide bonds previously  
 described. The urea or carbamate compound **213** can be  
 prepared from reacting the aniline **210** with an appropriately  
 substituted isocyanate or chloroformate respectively. The  
 compounds of Scheme 5 can be converted to their

corresponding hydroxamic acids by methods described in Scheme 2.

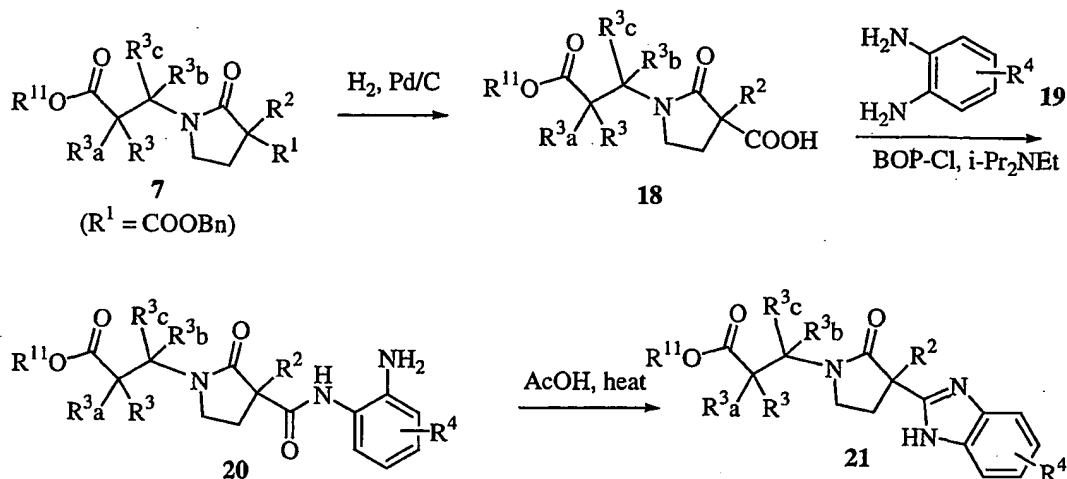
Scheme 5



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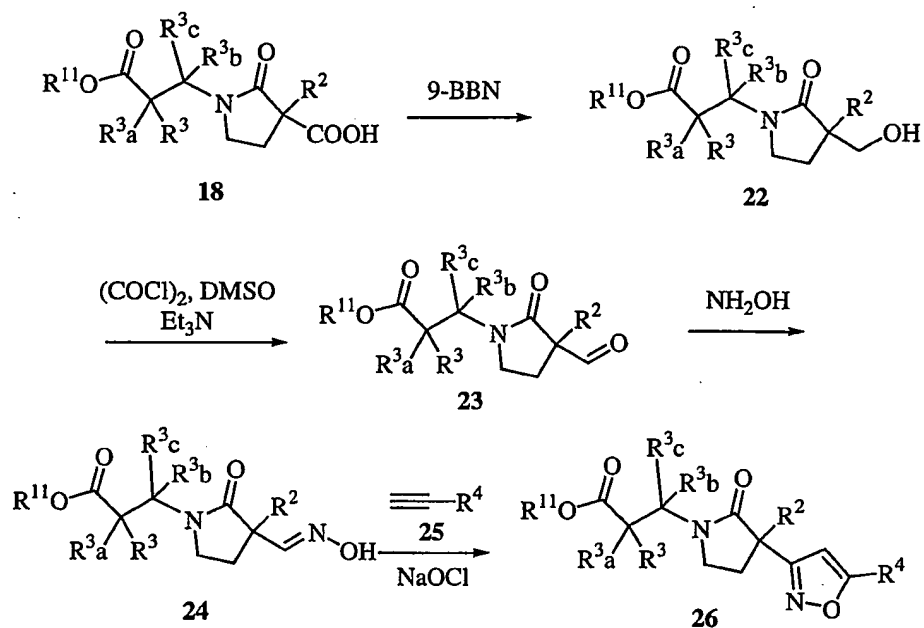
A variety of heterocyclic substituted lactams are prepared from 7 when R<sup>1</sup> is carbobenzyloxy group. As a representative example, scheme 6 illustrates the synthesis of the benzimidazole series. Following hydrogenolysis of 7, the resultant acid 18 is coupled with diamine 19 with coupling reagents such as BOP-Cl. Upon heating of 20 in acetic acid, benzimidazole 21 is formed. Ester 21 is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

Scheme 6



A series of isoxazole-substituted lactams of formula **26** is prepared using common intermediate **18** following the sequence outlined in Scheme 7. The carboxylic acid **18** is converted to aldehyde **23** by hydroboration and Swern oxidation. Oxime formation, in situ oxidation and [3+2] dipolar cycloaddition with acetylene **25** provides isoxazole **26**. Ester **26** is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

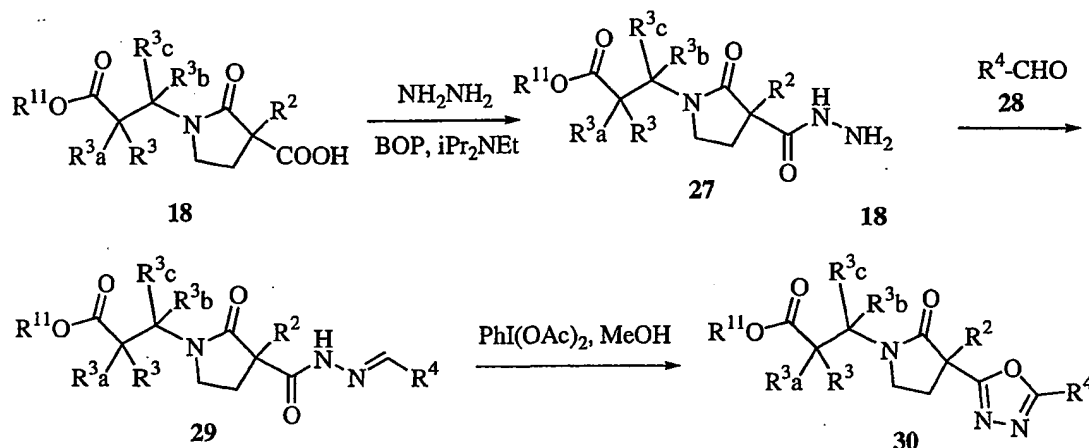
Scheme 7



Another series of lactams of formula **30** with an  
 5 oxadiazole substituent at the  $\alpha$  position is prepared using  
 common intermediate **18** following the sequence outlined in  
 Scheme 8. Acid **18** is first coupled with hydrazine to give  
**27**. Condensation with aldehyde **28** and oxidative cyclization  
 with  $\text{PhI}(\text{OAc})_2$  provided oxadiazole **30** (Yang, R. Y.; Dai, L.  
 10 X. J. Org. Chem. **1993**, 58, 3381). Ester **30** is converted to  
 the hydroxamic acid following the sequences outlined in  
 Scheme 2.

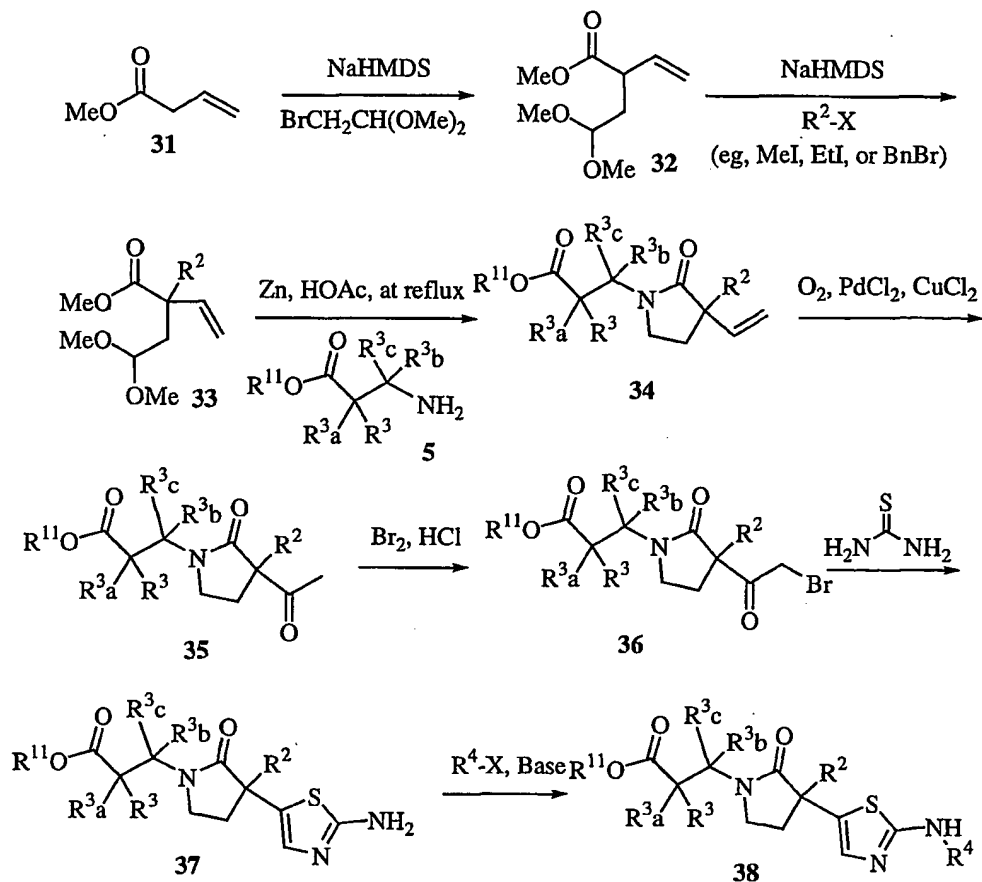


Scheme 8



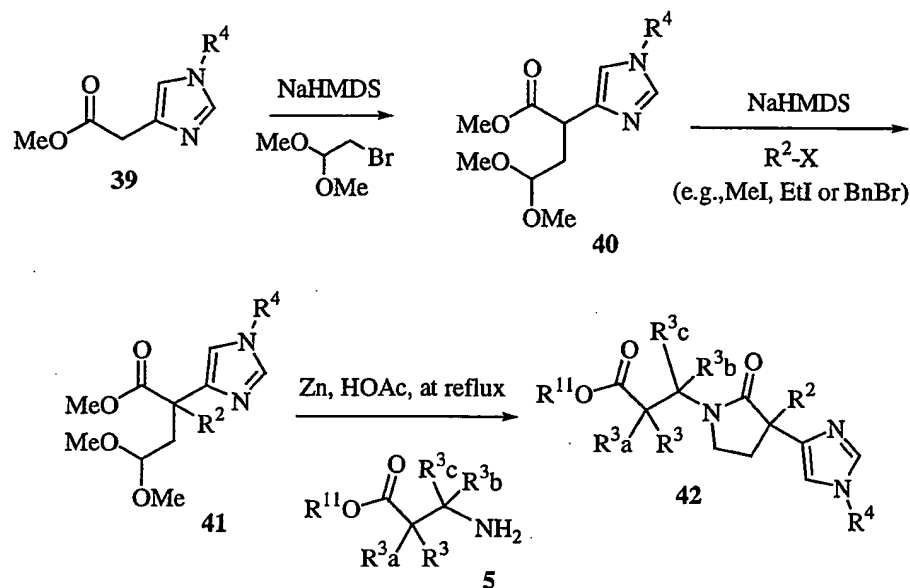
Another series of lactams of formula 38 with an  
 5 aminothiazole substituent at the  $\alpha$  position is prepared  
 following the sequence outlined in Scheme 9. Consecutive  
 alkylations with bromoacetaldehyde dimethyl acetal and  $\text{R}^2\text{-X}$   
 gives 33. Reaction of 33 with  $\beta$ -amino acid 5 using zinc in  
 acetic acid provides lactam 34. Bromoketone 36 is obtained  
 10 from 34 by Wacker oxidation and bromination. Treatment of  
 bromoketone 36 with thiourea produces aminothiazole 37  
 (Markees, D. G.; Burger, A. J. *Am. Chem. Soc.* **1948**, 70,  
 3329). Alkylation with  $\text{R}^4\text{-X}$  then provides 38. Ester 38 is  
 converted to the hydroxamic acid following the sequences  
 15 outlined in Scheme 2.

Scheme 9



Another series of lactams of formula 42 with an  
 5 imidazole substituent at the  $\alpha$  position is prepared  
 following the sequence outlined in Scheme 10. Consecutive  
 alkylations with bromoacetaldehyde dimethyl acetal and  $\text{R}^2\text{-X}$   
 gives 41. Reaction of 41 with  $\beta$ -amino acid 5 using zinc in  
 acetic acid provides lactam 42. Ester 42 is converted to  
 10 the hydroxamic acid following the sequences outlined in  
 Scheme 2.

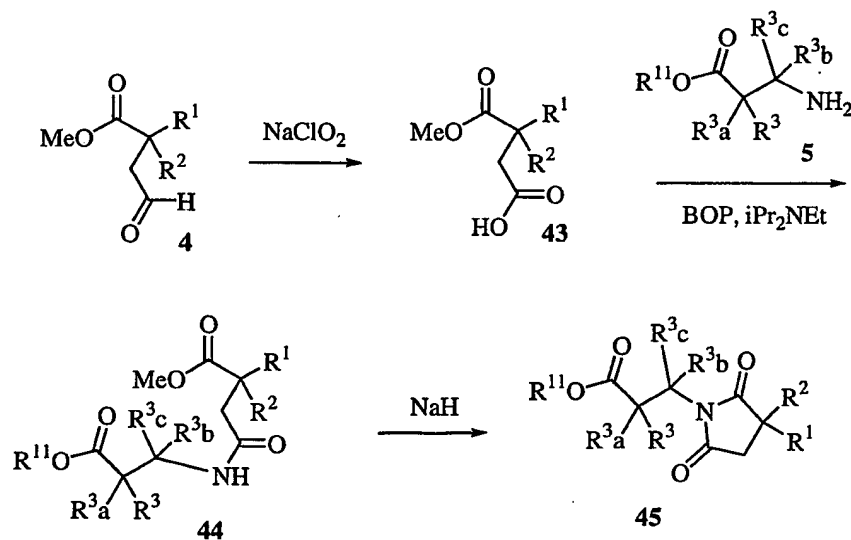
Scheme 10



A series of succinimides of formula 45 is prepared from intermediate 4 (Scheme 11). The synthesis entails oxidation to carboxylic acid 43, coupling with  $\beta$ -amino acid 5, and succinimide formation. Ester 45 is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

10

Scheme 11

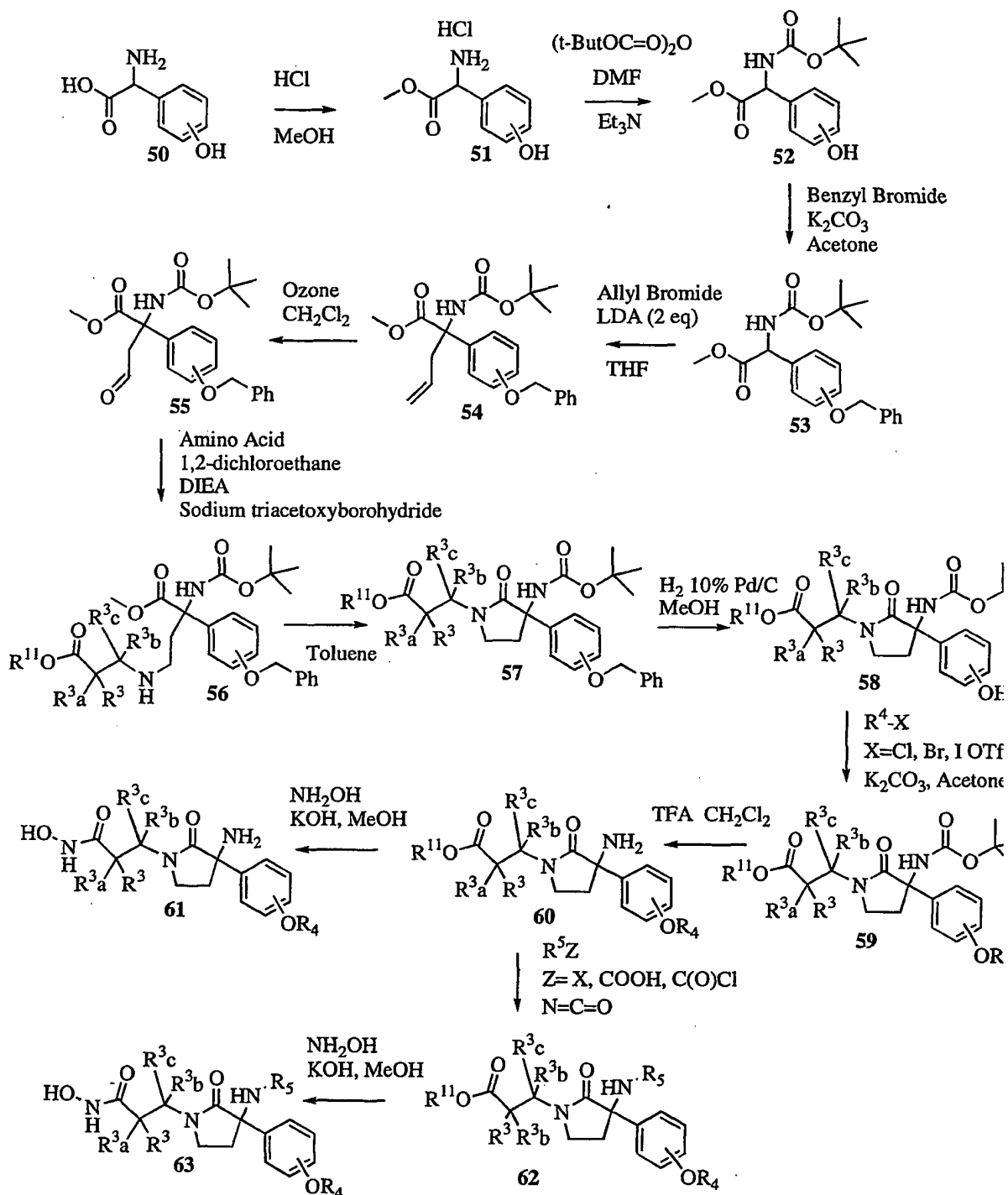


A variety of compounds of formula I wherein  $R^2$  is NHR can be prepared by methods described in Scheme 12. The hydroxyglycine acid was converted to the methyl ester using methanol and HCl to give compound 51, which was converted to the N-Boc protected amino acid 52 by methods described in the literature. The benzyloxyphenylglycine compound 53 was prepared by reacting the phenol compound 52 with benzyl bromide in acetone with a base such as potassium carbonate. The 2-allyl phenyl acetic acid compound 54, was prepared by treating compound 53 with LDA (2 eq) and allyl bromide. The olefin compound 54 is oxidized to the aldehyde compound 55 using ozone and triphenylphosphine, then reacted with an appropriate amine to give the imine, which can be reduced with reagents similar to sodium triacetoxyborohydride, to give the amine compound 56. The  $\gamma$ -lactam compound 57 is prepared by heating the amine compound 56 in an appropriate solvent such as toluene. The benzyl ether is removed by methods well known in the literature such as hydrogenation using palladium on carbon in hydrogen, to give compound 58. The compound 59 is prepared by reacting the phenol 58 with an appropriately substituted halide or the like in acetone with a base such as potassium carbonate. The hydroxamic acid compound 61 was prepared from compound 59 by methods well known in the literature for removing N-Boc groups and conversion of the methyl ester previously described. Alternatively the amine compound 60 can be treated with appropriately substituted acid chloride, isocyanate, carboxylic acid with coupling agents such as carbonyldiimidazole or the like, that are well known in the literature for making amide bonds. Alternatively the amine of compound 60 can be converted to an isocyanate by a variety of methods known in the literature like using phosgene and a base such as sodium carbonate, and reacting

this with an appropriately substituted amine, to give compound **62**. The hydroxamic acid was prepared by methods previously described.

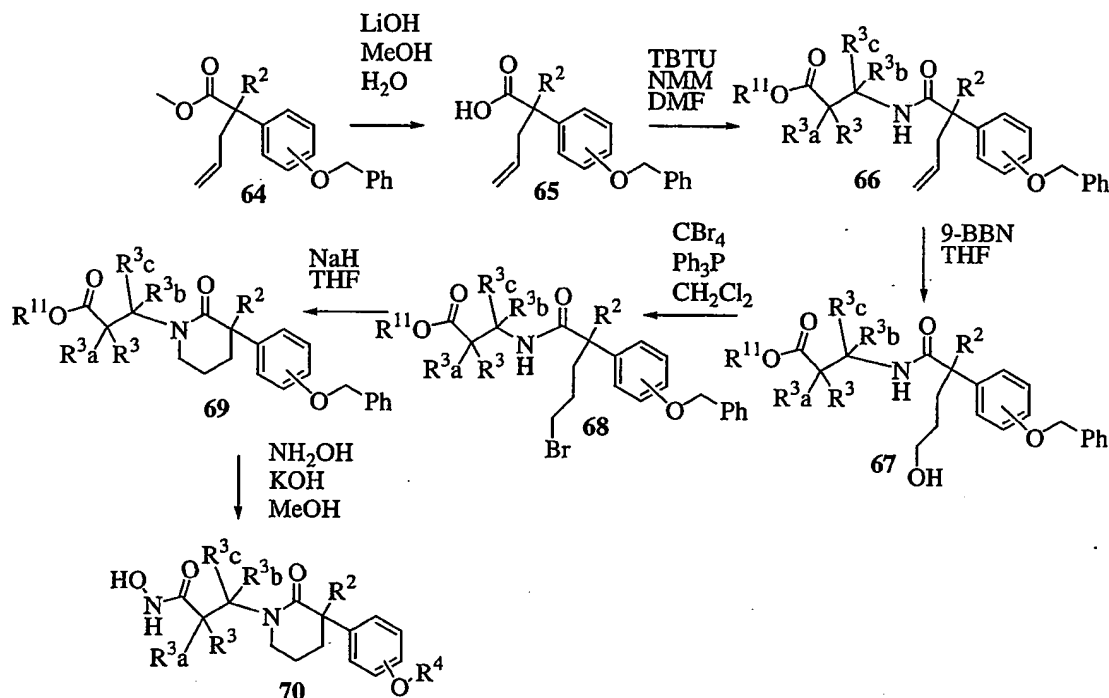
5

Scheme 12



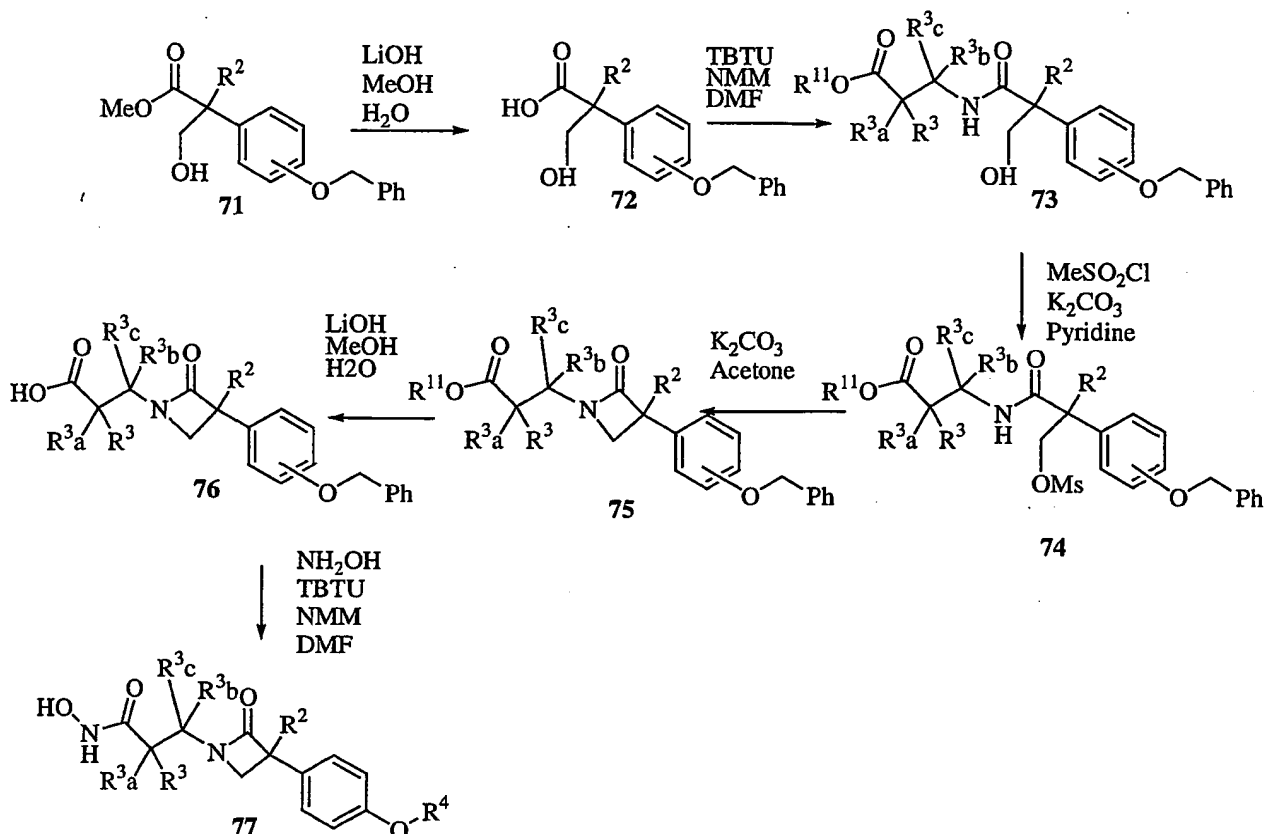
A variety of compounds of formula I wherein the lactam is a six member ring can be prepared by methods described in Scheme 13. The ester compound **64** is converted to the acid compound **65** by methods well known in the literature, such as lithium hydroxide in methanol water, then coupled to an appropriately substituted amine by methods well described in the literature for making amide bonds, such as TBTU and N-methyl morpholine in DMF, to give compound **66**. The hydroxy compound **67** was prepared from the olefin compound **66** by reduction with 9-BBN and oxidative workup with hydrogen peroxide. The  $\delta$ -lactam **69** is prepared by converting the hydroxy of compound **67** to a leaving group by methods well known in the literature such as carbon tetrabromide and triphenylphosphine in methylene chloride. The bromide compound **68** was reacted with a base such as sodium hydride in THF to give the  $\delta$ -lactam **69**. The hydroxamic acid compound **70** was prepared by methods previously described.

Scheme 13



A variety of compounds of formula I wherein the lactam  
 5 is a four member ring can be prepared by methods described  
 in Scheme 14. The ester compound **71** was converted to the  
 acid compound **72** and coupled to an appropriately substituted  
 amine by methods well known in the literature and previously  
 described. The  $\beta$ -lactam **75** is prepared by converting the  
 10 hydroxy of compound **73** to a leaving group by methods well  
 known in the literature, such as methanesulfonyl chloride  
 and potassium carbonate in pyridine. The methanesulfonate  
 compound **74** was reacted with a base such as potassium  
 carbonate in acetone to give the  $\beta$ -lactam **75**. The  
 15 hydroxamic acid compound **77** was prepared by methods  
 previously described.

Scheme 14

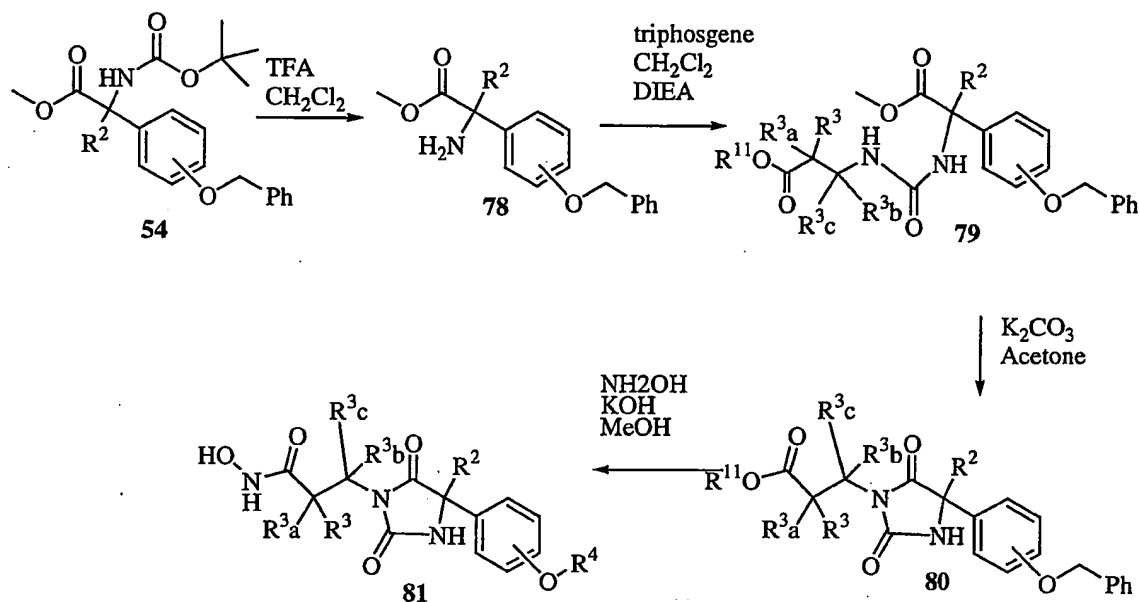


A variety of compounds of formula I wherein the lactam is replaced with a hydantoin ring can be prepared by methods described in Scheme 15. The amine compound **78** was prepared from the N-Boc compound **54** by methods previously described for the removal of Boc protecting groups. The urea compound **79** was prepared by converting the amine compound **78** to an isocyanate by methods well known in the literature and previously described, such as triphosgene and DIEA in methylene chloride and reacting this with an appropriately substituted amine. Alternatively, the amine **78** can be reacted with an isocyanate that is commercially available or can be prepared as described above. The hydantoin compound **80** was prepared by reacting the urea compound **79** with potassium carbonate in acetone. The final hydroxamic acid



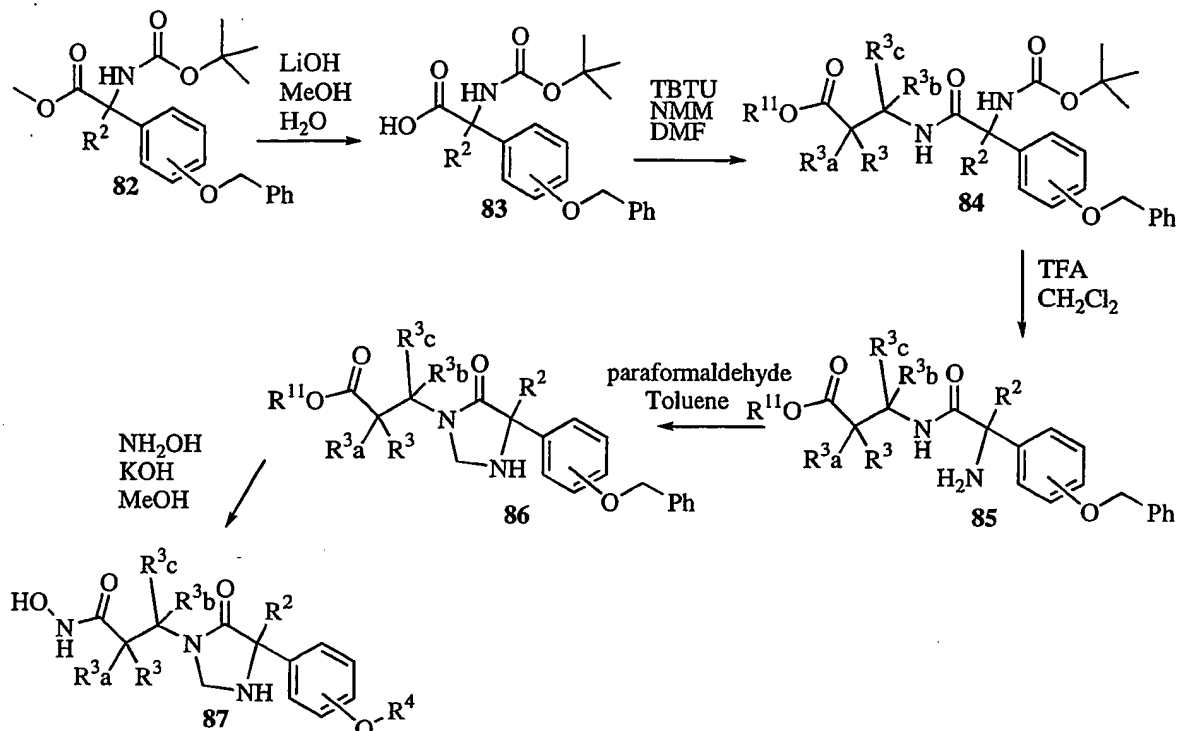
compound **81** was prepared by methods well documented previously.

Scheme 15



A variety of compounds of formula I wherein the lactam is replaced with a imidazolinone can be prepared by methods described in Scheme 16. Compound **84** was prepared from the phenylglycine compound **82**, by hydrolysis to the acid and coupling to an appropriately substituted amine as well described in the literature and previously detailed. The N-Boc group is removed by conventional methods previously described to give the amine compound **85**. The heterocyclic compound **86** was prepared by reacting the amine compound **85** with paraformaldehyde in toluene at elevated temperatures. The final hydroxamic acid compound **87** was prepared by methods well documented previously.

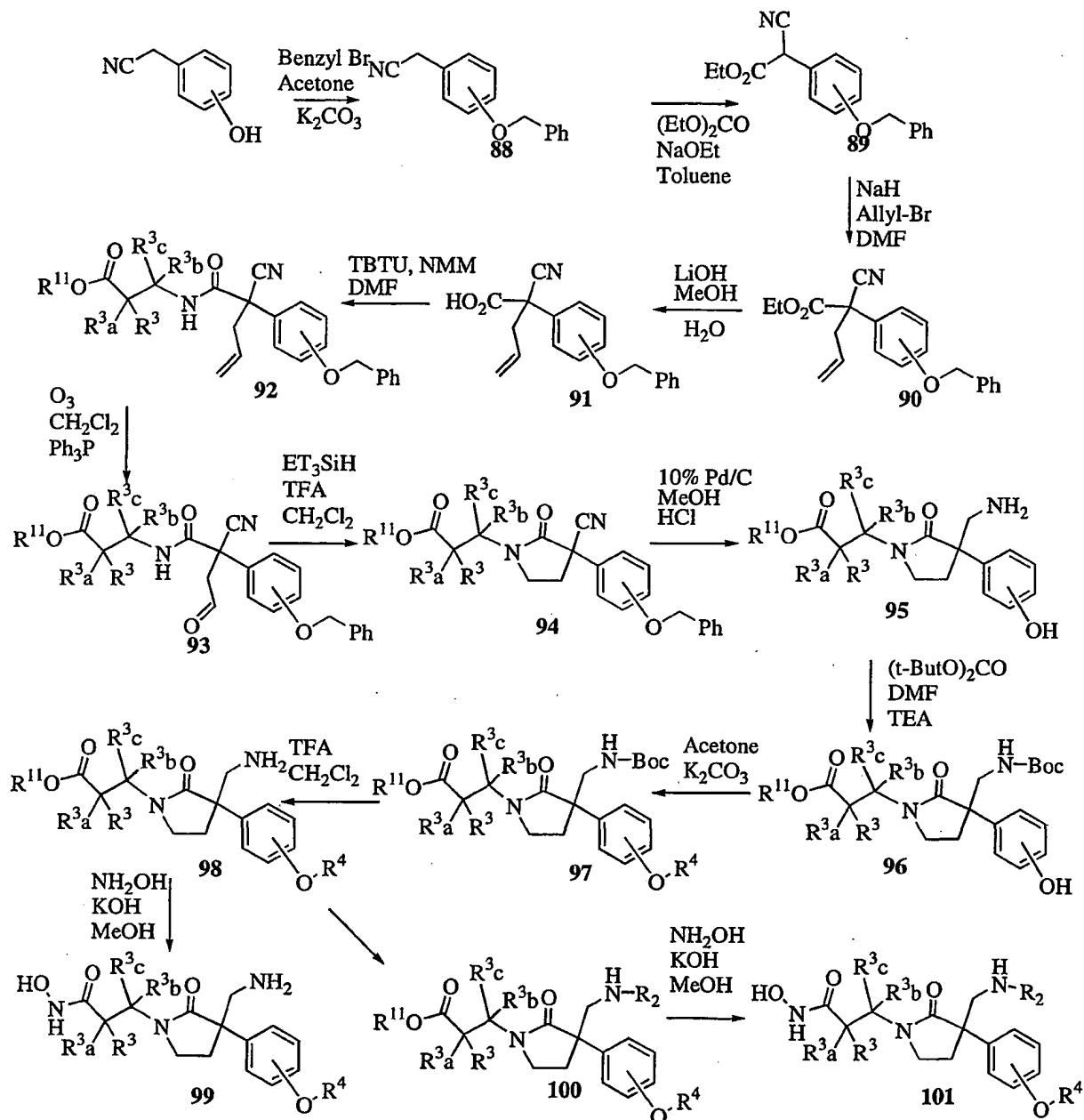
Scheme 16



- 5        A variety of compounds of formula I wherein  $\text{R}^2$  is  $\text{CH}_2\text{NHR}$  can be prepared by methods described in Scheme 17. The cyanoacetate compound 89 was prepared by reacting the hydroxyphenylacetonitrile with benzyl bromide in acetone with potassium carbonate to give compound 88, which was in
- 10      turn reacted with sodium ethoxide and diethylcarbonate in toluene at elevated temperatures. The allyl cyanoacetate compound 90 was prepared from the cyanoacetate compound 89 by generating the anion with a base such as sodium hydride and reacting this with allyl bromide in DMF. The nitrile
- 15      lactam compound 94 was prepared by a sequence of steps previously described in several other Schemes. The N-Boc methyleneamine compound 96 was prepared by reduction of the nitrile lactam compound 94, using palladium on carbon with  $\text{HCl}$  in methanol, to give the amino compound 95 which was
- 20      then protected by conventional methods with a Boc group to

give compound **96**. The final hydroxamic acid compounds **99** and **101** were prepared by methods previously described.

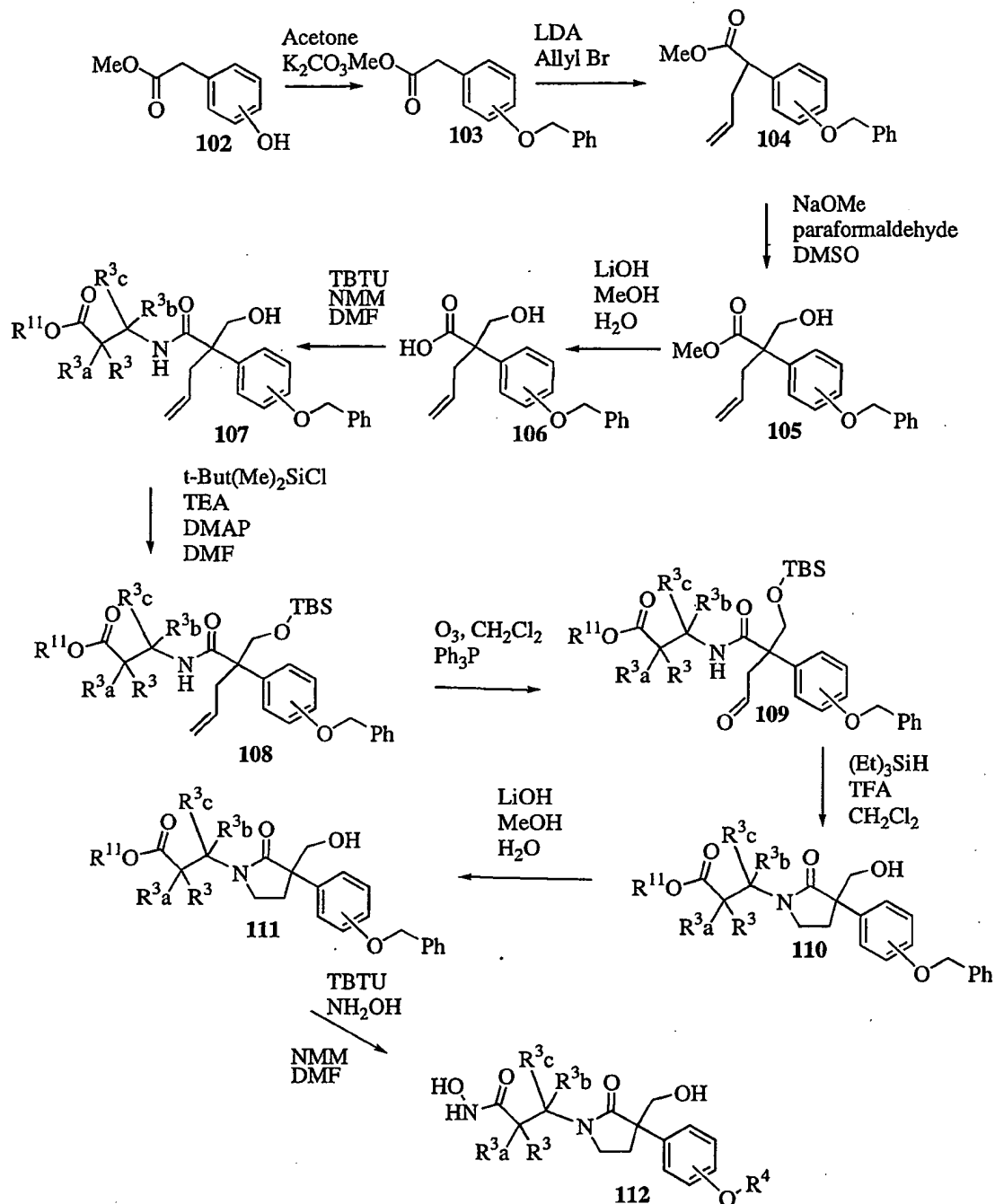
Scheme 17



A variety of compounds of formula I wherein  $R^2$  is  $CH_2OH$  can be prepared by methods described in Scheme 18. The allyl compound **104** was prepared from hydroxyphenyl acetate,

by reaction with benzyl bromide and potassium carbonate in acetone as previously described and then treating the benzyloxy phenyl acetate compound **103** with LDA and allyl bromide in THF. The methylene hydroxy compound **105** was  
5 prepared by treating the benzyloxy phenyl acetate compound **104** with paraformaldehyde and sodium methoxide in DMSO. The hydrolysis of the ester and coupling of the carboxylic acid to an appropriately substituted amine was described earlier to give the compound **107**. The protected O-silyl compound  
10 **108** was prepared by methods well described in the literature, then oxidation to the aldehyde compound **109** with ozone was described previously. The lactam compound **110** was prepared from the aldehyde compound **109** by treatment with triethylsilane and TFA in methylene chloride at ambient  
15 temperatures. The final hydroxamic acid compound **112** was prepared by methods previously described.

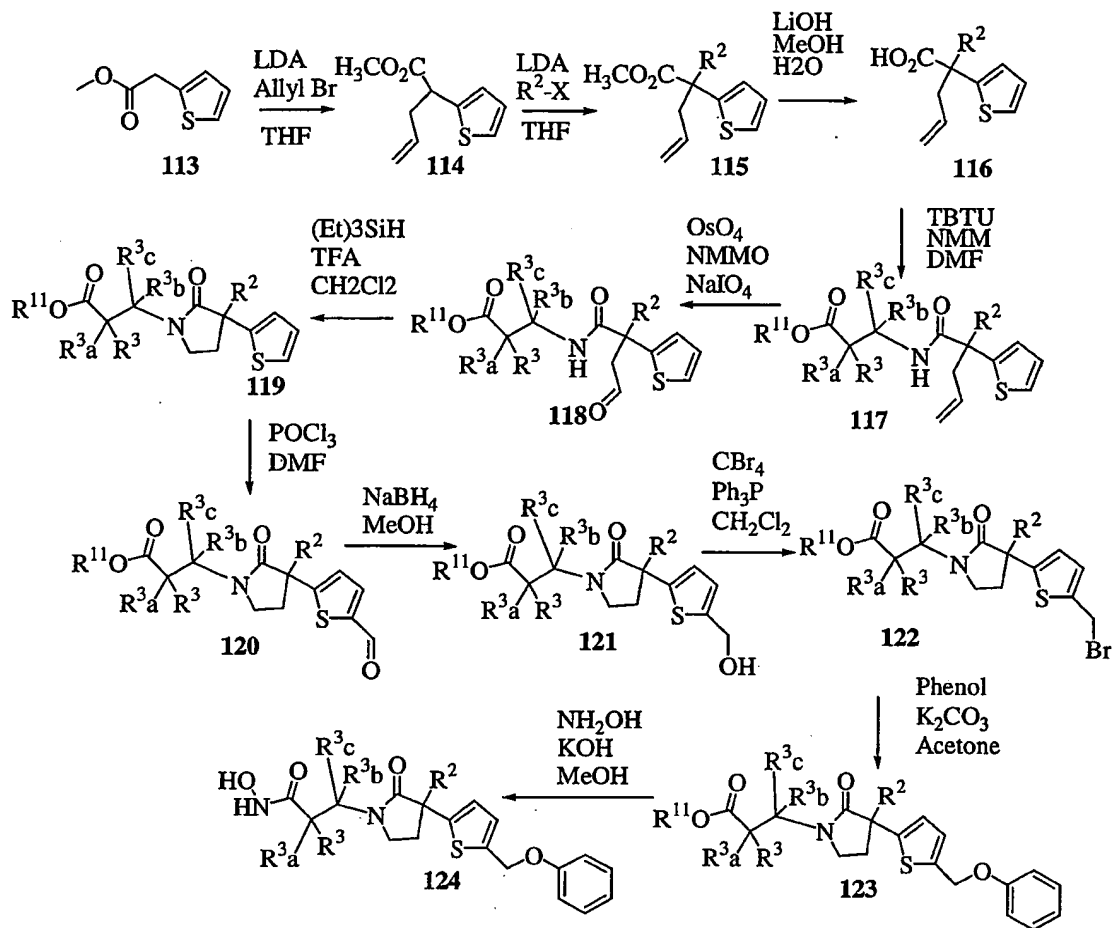
Scheme 18



A variety of compounds of formula I wherein  $R^1$  is a  
 5 heterocycle, such as thiophene, can be prepared by methods  
 described in Scheme 19. The thiophene substituted compound  
 115 was prepared by treating the thiophene acetate compound  
 113 with LDA and allyl bromide to give compound 114, and

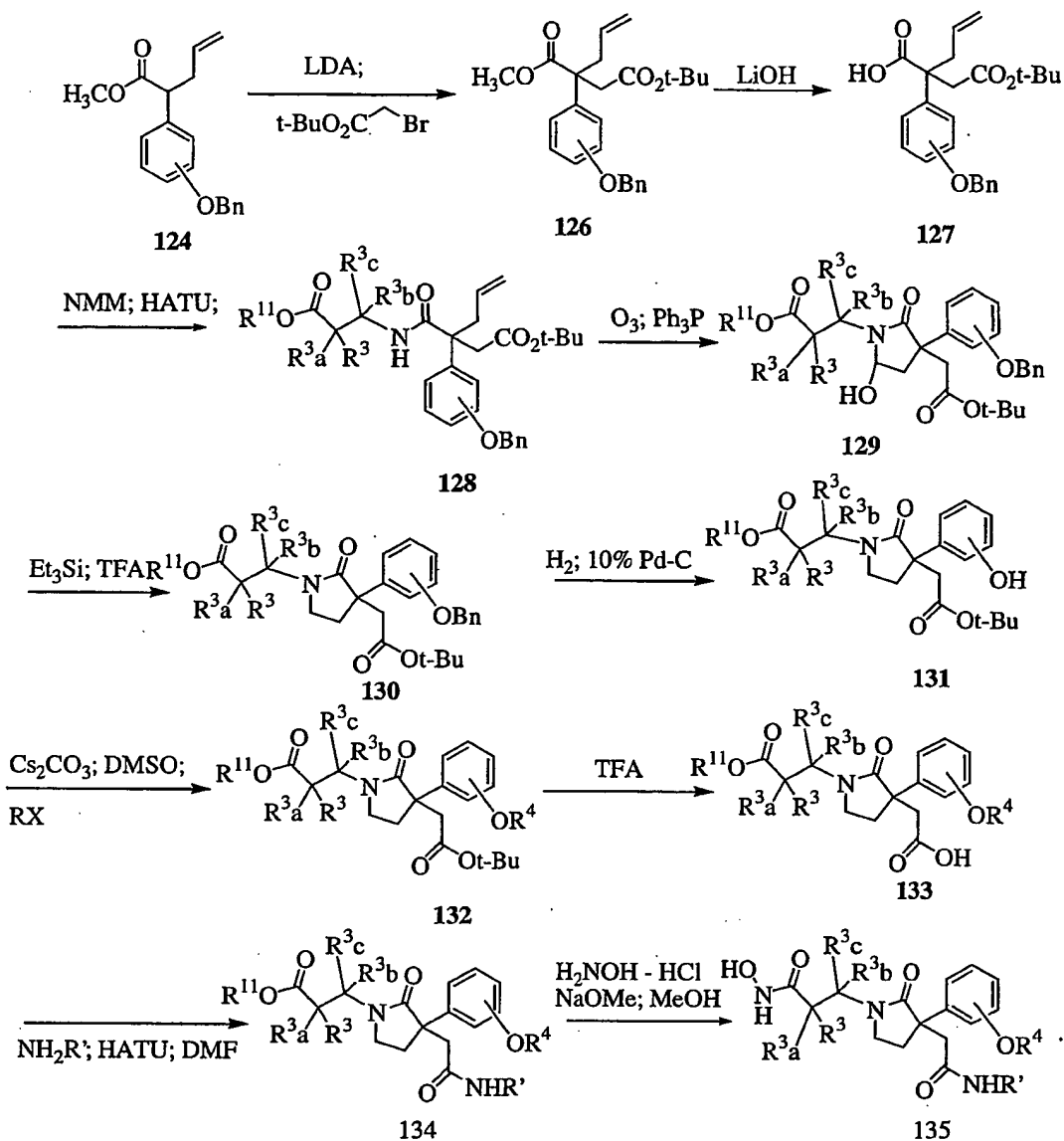
subsequently with LDA and methyl iodide in THF. The thiophene compound **117** was prepared by methods previously detailed for ester hydrolysis to the acid and coupling the carboxylic acid to an amine. The oxidation of the olefin compound **117**, to the aldehyde compound **118**, was performed by the action of osmium tetroxide and NMMO, to give the diol, then treatment with NaIO<sub>4</sub>. The formation of the lactam ring compound **119** was previously described using triethylsilane and TFA in methylene chloride. The aldehyde thiophene compound **120** was prepared by chemistry well described in the literature, using phosphorus oxychloride in DMF. The aldehyde compound **120** was reacted with sodium borohydride in methanol to give alcohol compound **121** that was reacted with carbon tetrabromide and triphenyl phosphine to give the bromide compound **122**. The bromide was treated with phenol and potassium carbonate in acetone to give the phenyl ether compound **123**. The final hydroxamic acid compound **124** was prepared by methods previously described.

Scheme 19



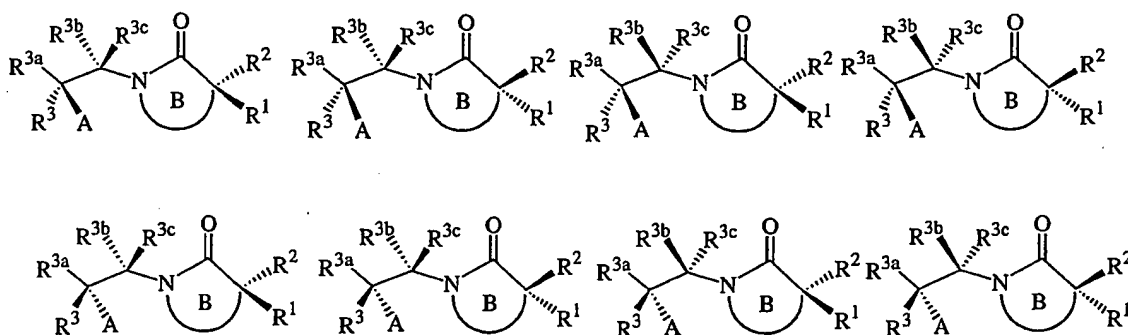
Another series of lactams of formula **135** is prepared  
 5 following the sequence outlined in Scheme 20. Ester **124** is  
 alkylated with *t*-butyl bromoacetate to give **126**. Ester **126**  
 is converted to **132** following previously described sequence.  
 Removal of *t*-butyl group and coupling with  $\text{NH}_2\text{R}'$  under  
 literature well known conditions gives **134**. Ester **134** is  
 10 converted to the hydroxamic acid following the sequences  
 outlined in Scheme 2.

Scheme 20



One diastereomer of a compound of Formula I may display  
 5 superior activity compared with the others. Thus, the  
 following stereochemistries are considered to be a part of  
 the present invention.





When required, separation of the racemic material can be  
 5 achieved by HPLC using a chiral column or by a resolution  
 using a resolving agent such as camphonic chloride as in  
 Steven D. Young, et al, *Antimicrobial Agents and*  
*Chemotherapy* **1995**, 2602-2605. A chiral compound of Formula  
 I may also be directly synthesized using a chiral catalyst  
 10 or a chiral ligand, e.g., Andrew S. Thompson, et al, *Tet.*  
*Lett.* **1995**, 36, 8937-8940).

Other features of the invention will become apparent in  
 the course of the following descriptions of exemplary  
 embodiments that are given for illustration of the invention  
 15 and are not intended to be limiting thereof.

### Examples

Abbreviations used in the Examples are defined as  
 follows: "1 x" for once, "2 x" for twice, "3 x" for thrice,  
 20 "°C" for degrees Celsius, "eq" for equivalent or  
 equivalents, "g" for gram or grams, "mg" for milligram or  
 milligrams, "mL" for milliliter or milliliters, "<sup>1</sup>H" for  
 proton, "h" for hour or hours, "M" for molar, "min" for  
 minute or minutes, "MHz" for megahertz, "MS" for mass  
 25 spectroscopy, "NMR" for nuclear magnetic resonance  
 spectroscopy, "rt" for room temperature, "tlc" for thin  
 layer chromatography, "v/v" for volume to volume ratio.

"a", "b", "R" and "S" are stereochemical designations familiar to those skilled in the art.

### Example 1

- 5                   **(1*S*-cis)-2-[3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-N-hydroxycyclohexanecarboxamide bis(trifluoroacetate) (salt)**
- (1a) Potassium t-Butoxide 1M in THF (80 mL) was added slowly to a solution of p-hydroxyphenyl glycine benzylimine (10.7 g, 36.2mmol) in THF (250mL) cooled to 0°C under a nitrogen atmosphere. The reaction was stirred for 1 h, then allyl bromide (4.38 g, 36.2 mmol) was added slowly giving a slurry. The reaction was stirred for an additional hour then 4-chloromethyl 2-methyl quinoline (6.93 g, 36.1 mmol) and tetrabutyl ammonium iodide (20 mol%) was added. The reaction mixture was allowed to warm to 40°C for 2 h then allowed to stir at RT overnight. 1N HCl (80 mL) and water (100 mL) were added to the reaction, stirred for 1 h and washed with ethyl ether (2X 100 mL). The organic layer was back washed with 1N HCl (50 mL). The combined aqueous layers were neutralized with sodium hydroxide (50%) and extracted with ethyl acetate (3 X 150 mL). The combined ethyl acetate layers were dried over magnesium sulfate and concentrated to give a dark oil. The oil was taken up in 125 mL ethanol and methanesulfonic acid (2 eq) was added. This was stirred at RT to give a precipitate. The solids were collected and dried to give 2-allyl p-hydroxyphenyl glycine (12.1 g, 70%) as a yellow powder MS (M+H)<sup>+</sup> =391.
- 30   (1b) Di-Boc (5.16 g, 23.68 mmol) was added to a solution of 2-allyl p-hydroxy phenyl glycine (1a) (11.5 g, 19.74 mmol), THF (100 mL), water (60 mL) and potassium carbonate (11.0 g, 78.9 mmol) at RT. The reaction was warmed to 60°C for 48 h.

The reaction was allowed to cool, diluted with ethyl acetate, washed with water, brine dried over magnesium sulfate and concentrated in vacuo. The product was purified by flash column chromatography on silica gel eluting hexane:  
5 ethyl acetate (60:40) to give the Boc protected phenyl glycine (7.5 g, 78%) as a white foam MS (M+H)<sup>+</sup> =491.

(1c) Osmium tetroxide (20 mol%) was added to a solution of the protected olefin (1b) (5.0 g, 10.2 mmol) and NMMO (1.79  
10 g, 15.3 mmol) in THF (75 mL) and water (20 mL). The reaction was stirred vigorously overnight, diluted with ethyl acetate (100 mL), washed with 10% NaHSO<sub>3</sub> (75 mL), brine, dried over magnesium sulfate and concentrated to give the intermediate diol. The diol was taken up in methylene  
15 chloride (75 mL) and sodium periodate 4.36 g, 20.4 mmol) in water (30 mL) was added. The reaction was stirred for 3 h and was diluted with methylene chloride (75 mL) and washed with water, brine, dried over magnesium sulfate and concentrated in vacuo to give the aldehyde (4.9 g, 97%) as a  
20 white foam MS (M+H)<sup>+</sup> =493.

(1d) The aldehyde (1c) (0.5 g, 1.02 mmol) was combined with methyl cis 2-amino cyclohexane carboxylate (0.24 g, 1.21 mmol) and diisopropyl ethyl amine (0.39 mL, 2.24 mmol) in  
25 1,2 dichloroethane (10 mL) at RT. The reaction was stirred for ½ h and the sodium triacetoxyborohydride was added. The reaction was stirred for 4 h, diluted with ethyl acetate, washed with brine, dried over magnesium sulfate and concentrated to give an oil. The crude amine was taken up  
30 in toluene (25 mL) under nitrogen and heated to reflux overnight. The reaction was concentrated and purified by flash chromatography on silica gel eluting methylene

chloride: ethyl acetate (60:40) to give the lactam (0.34 g, 56%) as a glass MS (M+H)<sup>+</sup> =588.

(1e) A solution of lithium hydroxide monohydrate (0.11 g, 2.7 mmol) in water (3 mL) was added to a solution of the lactam (1d) (0.32 g, 0.54 mmol) in methanol (15 mL) at RT. The reaction was warmed to 60°C for 4 h, allowed to cool and was made acidic (pH 6) with acetic acid. The reaction was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate and concentrated to give the carboxylic acid (0.28 g, 91%) as off white foam MS (M+H)<sup>+</sup> =574.

(1f) Isobutyl chloroformate (0.08 g, 0.58 mmol) was added to a solution of the carboxylic acid (1e) (0.28 g, 0.49 mmol), diisopropyl ethyl amine (0.19 g, 1.47 mmol) cooled to -30°C under a nitrogen atmosphere. The reaction was stirred for ½ h and the hydroxylamine hydrochloride (0.068 g, 0.98 mmol) dissolved in DMF (2 mL) and diisopropyl ethyl amine (0.19 g, 1.47 mmol) was added. The reaction was stirred for 1 h, taken up in ethyl acetate washed with brine, dried over magnesium sulfate and concentrated to give the hydroxamic acid (0.28 g, 100%) as an oil MS (M+H)<sup>+</sup> =589.

(1g) The Boc protected (1f) (0.28 g, 0.49 mmol) was taken up in methylene chloride (2 mL) and trifluoroacetic acid (2 mL) under nitrogen at RT. The reaction was stirred for 2 h, concentrated in vacuo and purified by reverse phase HPLC on a Vydac C-18 column, eluting with an acetonitrile:water:TFA gradient to give the title compound (0.11 g, 45%) as a white amorphous solid MS (M+H)<sup>+</sup> =489.

## Example 2

**(1S-trans)-2-[3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-N-hydroxycyclohexanecarboxamide bis(trifluoroacetate) (salt)**

- (2a) Following the procedures analogous to that used for the preparation of example (1a-1d), but using methyl trans-2-aminocyclohexanecarboxylate in step (1d) the protected lactam was prepared (0.22 g, 81%) as a white foam. MS (M+H)<sup>+</sup> =588.
- (2b) Following the procedures analogous to that used for (1g) but using the Boc protected lactam (2a) (0.22 g, 0.37 mmol) the cyclohexane methyl ester (0.21 g, 80%) was prepared as a glass MS (M+H)<sup>+</sup> =488.
- (2c) A solution of potassium hydroxide (2.81 g, 1.5 eq) in methanol (7 mL) was added to a hot solution of hydroxylamine hydrochloride (2.34 g, 33.7 mmol) in methanol (12 mL). After the mixture was cooled to room temperature, the precipitate was removed by filtration. The filtrate was used fresh and assumed hydroxylamine concentration of 1.76 M. The freshly prepared 1.76 M solution of hydroxylamine (1 mL) was added to the methyl ester from (2b) (0.05 g, 0.07 mmol) in methanol (1 mL) at RT. After 1 h at this temperature the reaction was complete. It was acidified to pH 6-7 with TFA and concentrated. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product (0.03 g, 60%) as a white amorphous solid. MS (M+H)<sup>+</sup> =489, MS (M-NH<sub>2</sub>)<sup>+</sup> =472

30

**Example 3**

**(1S-trans)-2-[3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-**

**pyrrolidinyl]cyclohexanecarboxylic acid  
bis(trifluoroacetate) (salt)**

(3a) Following the procedures analogous to that used for the preparation of example (1a-e and 1g), but using methyl  
5 trans-2-aminocyclohexanecarboxylate in step (1d) and the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the carboxylic acid product (0.12 g, 34%) as a white amorphous solid. MS  
10  $(M+H)^+ = 474$ , MS  $(M-NH_2)^+ = 457$ .

**Example 4**

**(1S-cis)-2-[(3S)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]cyclopentanecarboxylic acid  
15 bis(trifluoroacetate) (salt)**

(4a) Following the procedures analogous to that used for the preparation of example (1a-d), but using methyl cis-2-aminocyclopentanecarboxylate in step (1d) the protected  
20 cyclopentyl  $\gamma$ -lactam compound (2.1 g, 50%) was prepared as a white foam MS  $(M+Na)^+ = 596$ .

(4b) The protected cyclopentyl  $\gamma$ -lactam compound (1.9 g, 3.3 mmol) was dissolved in concentrated hydrochloric acid (30  
25 mL) and heated to 60°C for 6 h. The reaction was allowed to cool to RT taken up in acetonitrile (50 mL) and reconcentrated (3X) to give a yellow powder. The crude compound (0.20 g) was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA  
30 gradient, to give the title carboxylic acid product (0.12 g, 60%) as a white amorphous solid MS  $(M+H)^+ = 460$ .

**Example 5**

(1*S*-*cis*)-2-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxycyclopentanecarboxamide bis(trifluoroacetate) (salt)

(5a) The carboxylic acid compound from (4b) (1.4 g, 2.63 mmol) was combined with the BOP coupling agent (1.7 g, 3.9 mmol), hydroxylamine hydrochloride (1.8 g, 26 mmol) and diisopropyl ethyl amine (6.8 mL, 39 mmol) in DMF (50mL) under nitrogen at RT. The reaction was stirred for 24 h, concentrated *in vacuo* to give an oil. The oil was triturated in acetonitrile (50 mL) and TFA (3 mL) to give a powder. The solids were taken up in water, washed with ethyl acetate (2X), and the pH was adjusted to 7.5 to give a precipitate. The solids were collected and dried to give the title compound (0.95 g, 77%) as an off white solid MS (M+H)<sup>+</sup> =475.

#### Example 6

(1*R*-*trans*)-2-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxycyclopentanecarboxamide bis(trifluoroacetate) (salt) (6a) Following the procedures analogous to that used for the preparation of example (4a), and (2b,2c) the racemized hydroxamic compound was prepared. The crude *trans* compound was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the title hydroxamic acid product (0.08 g, 32%) as a white amorphous solid MS (M+H)<sup>+</sup> =475.

#### Example 7

(1*S*-*cis*)-2-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxy-4,4-dimethylcyclopentanecarboxamide bis(trifluoroacetate) (salt)

(7a) Triethyl amine (1.1 mL, 7.89 mmol) was added slowly to a clear solution of dimedone (1.0 g, 7.13 mmol) and trisylazide (3.3 g, 10.69 mmol) in methylene chloride (30 mL), cooled in an ice bath under a nitrogen atmosphere. The reaction was allowed to stir for 1 h and warmed to RT for an additional 3 h. The reaction was concentrated to give an oil. The product was purified by flash chromatography on silica gel eluting hexane: ethyl acetate (70:30) to give the diazodimedone compound (1.1 g, 92%) as an oil MS ( $M+CH_3CN$ )<sup>+</sup> =208.

(7b) The diazodimedone (7a) (1.1 g, 6.6 mmol) was dissolved in methanol (100 mL) in a quartz flask. The reaction was irradiated in a UV light chamber for 3 h. The reaction was concentrated to give the methyl 2-oxo-4,4-dimethylcyclopentylcarboxylate (1.1 g, 100%) as an oil MS ( $M+H$ )<sup>+</sup> =171.

(7c) O-benzyl hydroxylamine hydrochloride (2.46 g, 15.4 mmol) was added to a solution of methyl 2-oxo-4,4-dimethylcyclopentylcarboxylate (1.1g, 6.4 mmol) in methanol (30 mL) and potassium carbonate (4.25 g, 30.8 mmol). The reaction was stirred overnight, becoming a thick slurry. This was diluted with ethyl acetate filtered, washed with water, brine, dried over magnesium sulfate and concentrated to give an oil. The product was purified by flash chromatography on silica gel eluting hexane: ethyl acetate (90:10) to give the oxime (1.2 g, 68%) as an oil MS ( $M+H$ )<sup>+</sup> =276.

(7d) The oxime (7c) was taken up in methanol (50 mL) and HCl conc. (2 mL) in a Parr shaker bottle. The reaction was degassed, 10% Pd/C (1 g), was added and charged to 60 psi



hydrogen pressure. The reaction was shaken over night, filtered and concentrated to give the methyl 2-amino-4,4-dimethylcyclopentanecarboxylate (0.71 gm, 93%) as an oil MS  $(M+H)^+ = 172$ .

5

(7e) Following the procedures analogous to that used for the preparation of example (5), but using methyl 2-amino-4,4-dimethylcyclopentanecarboxylate for (4a) the title compound was prepared. The crude compound was purified by reverse  
10 phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile: water: TFA gradient, to give the title hydroxamic acid product (0.10 g, 37%) as a white amorphous solid MS  $(M+H)^+ = 503$ .

15

#### Example 8

**(1*S*-cis)-1-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-2,3-dihydro-*N*-hydroxy-1*H*-indene-2-carboxamide  
bis(trifluoroacetate) (salt)**

20

(8a) Methyl acetoacetate (2.0 g, 15.3 mmol) was added to a solution of sodium ethoxide (3.1 g, 45.9 mmol) and ethanol (50 mL) under nitrogen at RT. The reaction was stirred for ½ h and the bromomethyl benzonitrile (3.0 g, 15.3 mmol) was  
25 added. The reaction was heated to reflux overnight, allowed to cool, concentrated, the residue was taken up in ethyl acetate washed with water, brine, dried over magnesium sulfate and concentrated to give an oil. The oil was purified by flash chromatography on silica gel eluting  
30 hexane: ethyl acetate (80:20) to give the olefin product (1.3 g, 43%) as an oil MS  $(M+H)^+ = 204$ .

- (8b) The olefin compound (8a) (1.62 g, 7.97 mmol) was dissolved in methanol, degassed with nitrogen, 10% Pd/C was added and the reaction was charged to 55 psi hydrogen. The reaction was shaken for 4 days, was filtered and concentrated to give a colorless oil. The product was purified by flash chromatography on silica gel eluting methylene chloride: methanol (95:5) to give the amino compound (1.5 g, 94%) as an oil MS (M+H)<sup>+</sup> =192.
- (8c) Following the procedures analogous to that used for the preparation of example (5), but using the amino compound from (8b) the title compound was prepared. The crude compound was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile: water: TFA gradient, to give the title hydroxamic acid product (0.05 g, 20%) as a white amorphous solid MS (M+H)<sup>+</sup> =523.

#### Example 9

**(3*R*-trans)-4-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-tetrahydro-*N*-hydroxy-3-furancarboxamide bis(trifluoroacetate) (salt)**

(9a) Dimethyl 3,4-furandicarboxylate (5.20 g, 28.0mmol) was combined with 5% Rhodium/C in methanol (30mL) and ethyl acetate (10mL) in a Parr shaker bottle. The reaction was charged to 50 psi hydrogen and was shaken for 8.5 h. The reaction was filtered over celite, concentrated in vacuo to give the dimethyl 3,4-tetrahydrofuran dicarboxylate (5.2 g, 100%) as an oil MS (M-CH<sub>3</sub>OH)<sup>+</sup> =156.

(9b) Lithium hydroxide (1.32 g, 31.4 mmol) dissolved in water (20 mL) was added to a solution of dimethyl 3,4-tetrahydrofuran dicarboxylate (9a) (5.2 g, 28.0 mmol) in methanol (40 mL) at RT under a nitrogen atmosphere. The

reaction was stirred for 4 h, concentrated, made acidic with 1N HCl and extracted with ethyl acetate (2X 100 mL). The combined organic layer was washed with brine, dried over magnesium sulfate and concentrated to give the mono acid  
5 (3.75 g, 77%) as an oil MS  $(M+H)^+ = 175$ .

(9c) Diphenylphosphorylazide (5.9 g, 21.5 mmol) was added to a solution of the mono acid (9b) (3.75 g, 21.5 mmol) in toluene (50 mL) and triethyl amine (4.3g, 43 mmol). The  
10 reaction was heated to 90°C for 2 h and then benzyl alcohol (3.4g, 32.2mmol) was added. The reaction was heated to 90°C overnight, cooled to RT, concentrated in vacuo, and partitioned between ethyl acetate and water. The combined organic layer was washed with brine, dried over magnesium  
15 sulfate and concentrated to give an oil. The product was purified by flash chromatography over silica gel eluting ethyl acetate:hexane (30:70) to give the N-protected methyl 3-amino-4-tetrahydrofurancarboxylate (3.30 g, 55%) as an oil MS  $(M+H)^+ = 280$ .

20

(9d) The N-protected methyl 3-amino-4-tetrahydrofurancarboxylate (9c) (3.30 g, 11.8 mmol) was taken up in methanol (50 mL) in a Parr shaker bottle. The reaction was degassed, 10% Pd/C (0.1 g) was added and  
25 charged to 60 psi hydrogen pressure. The reaction mixture was shaken for 1 h, filtered and concentrated to give the methyl 3-amino-4-tetrahydrofurancarboxylate (1.65 gm, 95%) as an oil MS  $(M+CH_3CN)^+ = 187$ .

30 (9e) Following the procedures analogous to that used for the preparation of example (1), but using methyl 3-amino-4-tetrahydrofurancarboxylate in step (1d) and procedures (2b-c) the title compound was prepared. The product was

purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product (0.12 g, 65%) as a white amorphous solid. MS (M+H)<sup>+</sup> =474.

5

**Example 10**

**(βR)-3-amino-N-hydroxy-β-(2-methylpropyl)-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinepropanamide bis(trifluoroacetate) (salt)**

10

(10a) Following the procedures analogous to that used for the preparation of example (9c,9d), but using mono t-butyl (D)-3-isopropylsuccinate in step (9c) and procedures (2b-c, 1f) the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product (0.05 g, 35%) as a white amorphous solid. MS (M+H)<sup>+</sup> =491.

15

20

**Example 11**

**(βR)-3-amino-β-(2-methylpropyl)-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinepropanoic acid bis(trifluoroacetate) (salt)**

(11a) Following the procedures analogous to that used for the preparation of example (9c,9d), but using mono t-butyl (D)-3-isopropylsuccinate in step (9c) and procedures (2b-c) the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the carboxylic acid product (0.05 g, 35%) as a white amorphous solid. MS (M+H)<sup>+</sup> =476.

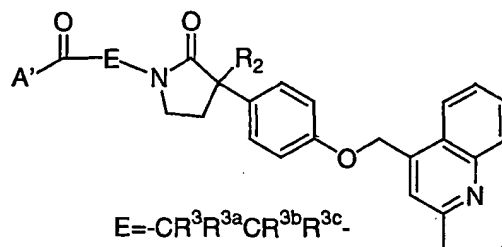
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**Example 12**

**3-amino-N-hydroxy- $\alpha,\alpha$ -dimethyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinepropanamide  
bis(trifluoroacetate) (salt)**

- 5 (12a) Following the procedures analogous to that used for the preparation of example (9c,9d), but using methyl 3-amino-2,2-dimethylpropanoate in step (9c) and procedures (2b-c, 1f) the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep
- 10 column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product (0.03 g, 30%) as a white amorphous solid. MS (M+H)<sup>+</sup> =463.

Table 1

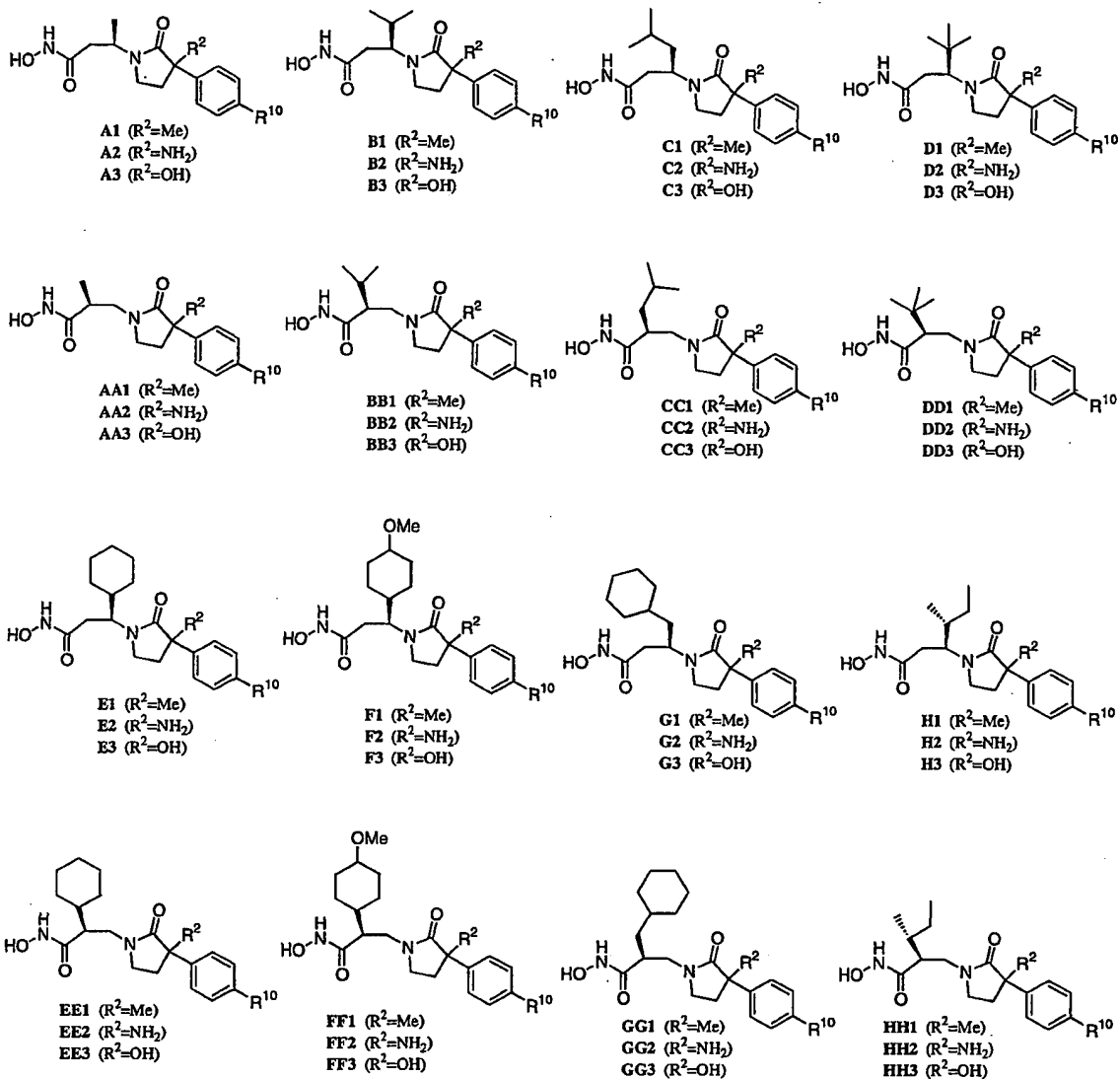


Ex	A'	E	R <sup>2</sup>	MS (M+H) <sup>+</sup>
1	NHOH		NH <sub>2</sub>	489
2	NHOH		NH <sub>2</sub>	489
3	OH		NH <sub>2</sub>	474
4	OH		NH <sub>2</sub>	460
5	NHOH		NH <sub>2</sub>	475
6	NHOH		NH <sub>2</sub>	475
7	NHOH		NH <sub>2</sub>	503
8	NHOH		NH <sub>2</sub>	523
9	NHOH		NH <sub>2</sub>	474
10	NHOH		NH <sub>2</sub>	491
11	OH		NH <sub>2</sub>	476
12	NHOH		NH <sub>2</sub>	463

5        The following tables contain representative examples of the present invention. Each entry in each table is intended to be paired with each formula at the start of the table.

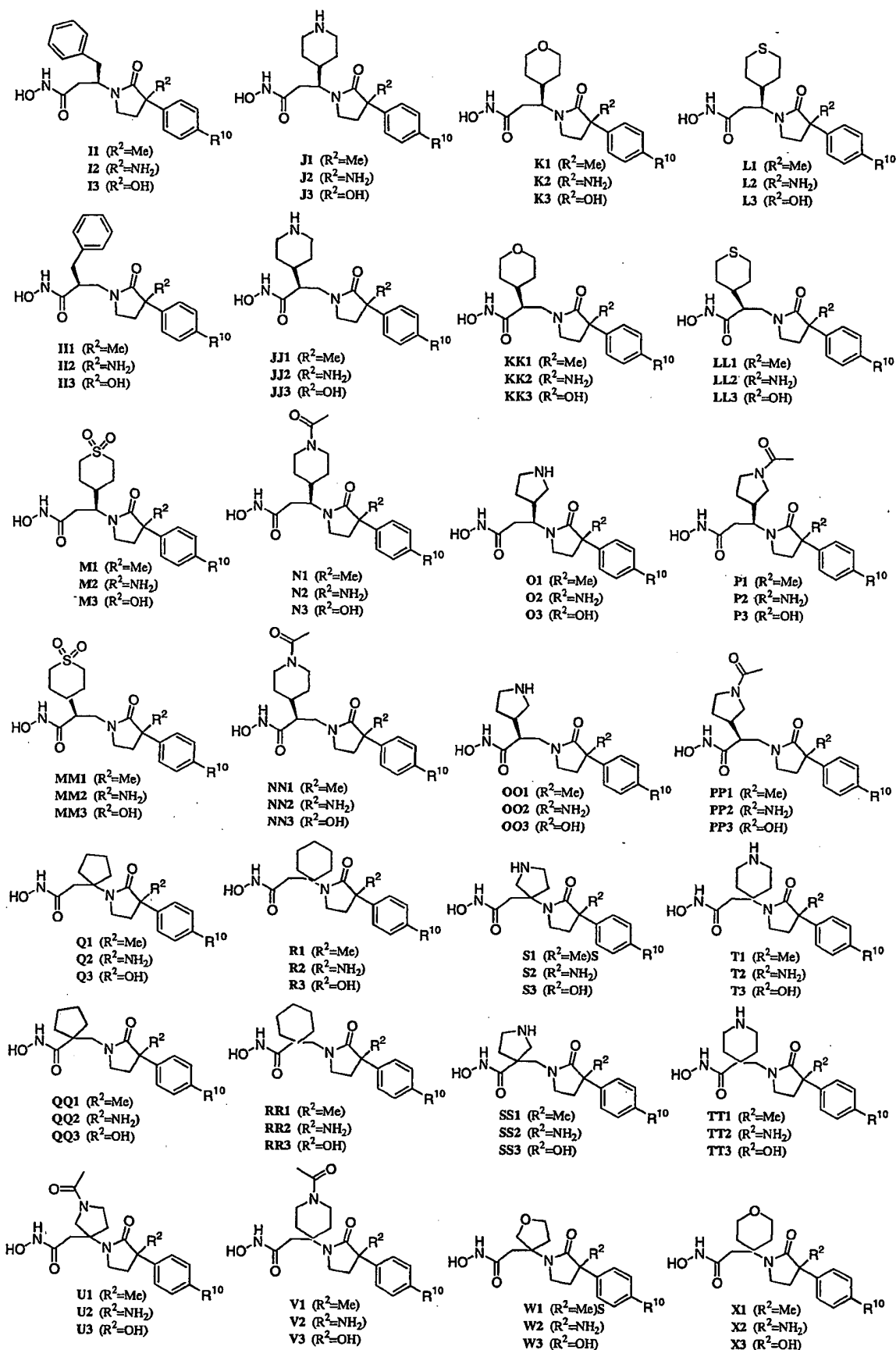
For example, in Table 2, example 1 is intended to be paired with each of formulae A1-HHH3.

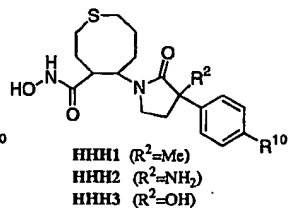
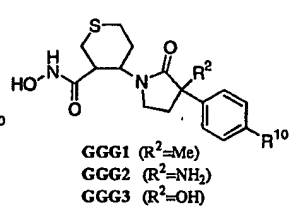
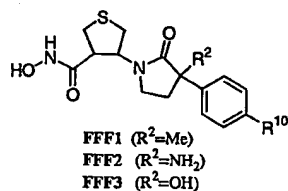
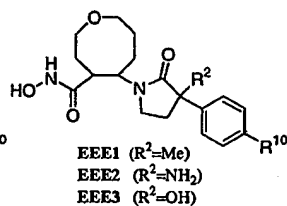
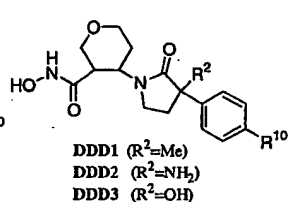
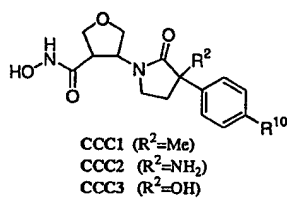
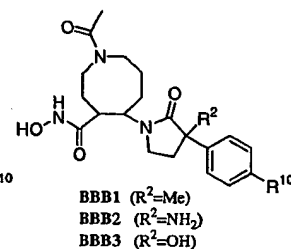
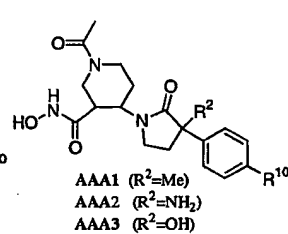
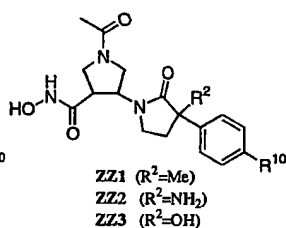
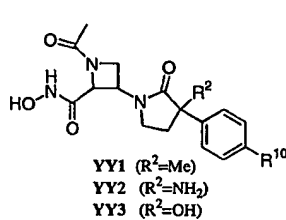
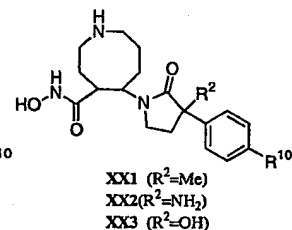
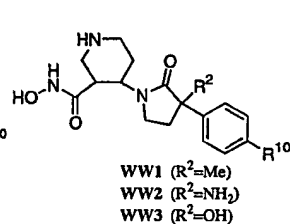
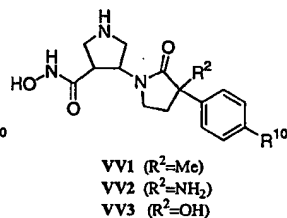
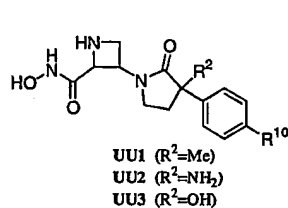
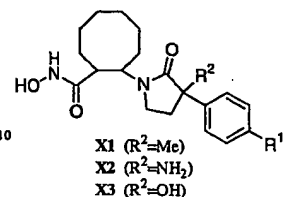
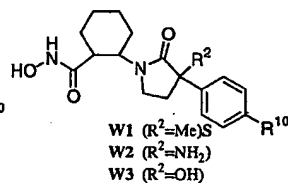
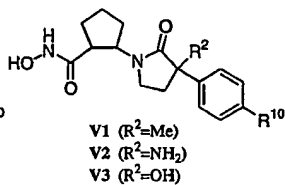
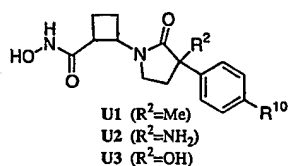
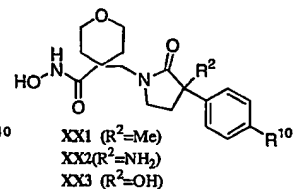
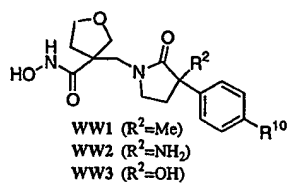
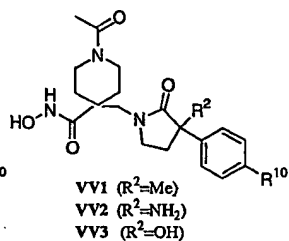
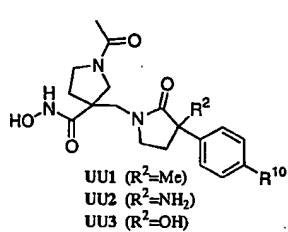
TABLE 2





5





Ex#	R <sup>10</sup>
-----	-----------------

1	H
2	methyl
3	methoxy
4	1-methylethyl
5	1-methylethoxy
6	phenyl
7	[1,1'-biphenyl]-4-yl
8	phenoxy
9	2-phenylethyl
10	2-(3,5-dimethylphenyl)ethyl
11	1-(2,6-dimethylphenyl)ethyl
12	2-phenylethenyl
13	phenoxymethyl
14	(2-methylphenyl)methoxy
15	(3-methylphenyl)methoxy
16	3-methylphenoxy
17	2,6-dimethylphenoxy
18	(2,6-dimethylphenyl)methoxy
19	3,5-dimethylphenoxy
20	(3,5-dimethylphenyl)methoxy
21	2-(3,5-dimethylphenyl)ethyl
22	2-(3,5-dimethylphenyl)ethenyl
23	(3-amino-5-methylphenyl)methoxy
24	(2-amino-6-methylphenyl)methoxy
25	(3-cyano-5-methylphenyl)methoxy
26	(3-cyano-5-methylphenoxy)methyl
27	(3-cyano-5-nitrophenyl)methoxy
28	(3,5-diethoxyphenyl)methoxy
29	(3,5-dimethoxyphenyl)methoxy
30	3,5-dimethoxyphenoxy
31	2-(3,5-dimethoxyphenyl)ethyl
32	1-(3,5-dimethoxyphenyl)ethoxy
33	(3,5-dichlorophenyl)methoxy
34	(2,6-dichlorophenyl)methoxy
35	(3,5-dibromophenyl)methoxy
36	3,5-dibromophenoxy
37	(3-amino-5-cyanophenyl)methoxy
38	[2,6-bis(trifluoromethyl)phenyl]methoxy
39	2,6-bis(trifluoromethyl)phenoxy
40	(3-aminocarbonyl-5-methylphenyl)methoxy
41	([1,1'-biphenyl]-2-yl)methoxy
42	([1,1'-biphenyl]-3-yl)methoxy
43	[5-methyl-3-(methylsulfonyl)phenyl]methoxy
44	5-methyl-3-(methylsulfonyl)phenoxy
45	(2-pyridinyl)methoxy
46	(4-pyridinyl)methoxy
47	(2,6-dimethyl-4-pyridinyl)methoxy

48	2,6-dimethyl-4-pyridinyloxy
49	1-(2,6-dimethyl-4-pyridinyl)ethoxy
50	(3,5-dimethyl-4-pyridinyl)methoxy
51	(2,6-diethyl-4-pyridinyl)methoxy
52	(2,6-dichloro-4-pyridinyl)methoxy
53	(2,6-dimethoxy-4-pyridinyl)methoxy
54	(2-chloro-6-methyl-4-pyridinyl)methoxy
55	(2-chloro-6-methoxy-4-pyridinyl)methoxy
56	(2-methoxy-6-methyl-4-pyridinyl)methoxy
57	(1-naphthalenyl)methoxy
58	1-naphthalenyloxy
59	(2-naphthalenyl)methoxy
60	(2-methyl-1-naphthalenyl)methoxy
61	(4-methyl-2-naphthalenyl)methoxy
62	(4-quinolinyl)methoxy
63	1-(4-quinolinyl)ethoxy
64	4-quinolinylloxy
65	(4-quinolinylloxy)methyl
66	2-(4-quinolinyl)ethyl
67	(2-methyl-4-quinolinyl)methoxy
68	2-methyl-4-quinolinylloxy
69	(2-chloro-4-quinolinyl)methoxy
70	(2-methoxy-4-quinolinyl)methoxy
71	(2-hydroxy-4-quinolinyl)methoxy
72	(2-trifluoromethyl-4-quinolinyl)methoxy
73	(2-phenyl-4-quinolinyl)methoxy
74	(2,6-dimethyl-4-quinolinyl)methoxy
75	(2,7-dimethyl-4-quinolinyl)methoxy
76	(5-quinolinyl)methoxy
77	(7-methyl-5-quinolinyl)methoxy
78	(7-methoxy-5-quinolinyl)methoxy
79	(8-quinolinyl)methoxy
80	2-(1,2,3-benzotriazol-1-yl)ethyl
81	(2-benzimidazolyl)methoxy
82	(1,4-dimethyl-5-imidazolyl)methoxy
83	(3,5-dimethyl-4-isoxazolyl)methoxy
84	(4,5-dimethyl-2-oxazolyl)methoxy
85	(2,5-dimethyl-4-thiazolyl)methoxy
86	(3,5-dimethyl-1-pyrazolyl)ethyl
87	(1,3-benzodioxo-4-yl)methoxy
88	(1,3,5-trimethyl-4-pyrazolyl)methoxy
89	(2,6-dimethyl-4-pyrimidinyl)methoxy
90	(4,5-dimethyl-2-furanyl)methoxy
91	(4,5-dimethyl-2-thiazolyl)methoxy
92	2-(2-oxazolyl)ethyl

## UTILITY

The compounds of formula I are expected to possess metalloproteinase and/or aggrecanase and/or TNF- $\alpha$  inhibitory activity. The MP inhibitory activity of the compounds of the present invention is demonstrated using assays of MP activity, for example, using the assay described below for assaying inhibitors of MP activity. The compounds of the present invention are expected to be bioavailable in vivo as demonstrated, for example, using the ex vivo assay described below. The compounds of formula I are expected to have the ability to suppress/inhibit cartilage degradation in vivo, for example, as demonstrated using the animal model of acute cartilage degradation described below.

The compounds provided by this invention should also be useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit MPs. These would be provided in commercial kits comprising a compound of this invention.

Metalloproteinases have also been implicated in the degradation of basement membranes to allow infiltration of cancer cells into the circulation and subsequent penetration into other tissues leading to tumor metastasis (Stetler-Stevenson, *Cancer and Metastasis Reviews* 1990, 9, 289-303). The compounds of the present invention should be useful for the prevention and treatment of invasive tumors by inhibition of this aspect of metastasis.

The compounds of the present invention should also have utility for the prevention and treatment of osteopenia associated with matrix metalloproteinase-mediated breakdown of cartilage and bone that occurs in osteoporosis patients.

Compounds that inhibit the production or action of TNF and/or Aggrecanase and/or MMP's are potentially useful for the treatment or prophylaxis of various inflammatory,

infectious, immunological or malignant diseases or conditions. Thus, the present invention relates to a method of treating various inflammatory, infectious, immunological or malignant diseases. These include acute infection, acute phase response, age related macular degeneration, alcoholism, anorexia, asthma, autoimmune disease, autoimmune hepatitis, Bechet's disease, cachexia (including cachexia resulting from cancer or HIV), calcium pyrophosphate dihydrate deposition disease, cardiovascular effects, chronic fatigue syndrome, chronic obstruction pulmonary disease, coagulation, congestive heart failure, corneal ulceration, Crohn's disease, enteropathic arthropathy (including inflammatory bowel disease), Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease, gingivitis, glucocorticoid withdrawal syndrome, gout, graft versus host disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious arthritis, inflammation, intermittent hydrarthrosis, Lyme disease, meningitis, multiple sclerosis, myasthenia gravis, mycobacterial infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory disease, periodontitis, polymyositis/dermatomyositis, post-ischaemic reperfusion injury, post-radiation asthenia, psoriasis, psoriatic arthritis, pyoderma gangrenosum, relapsing polychondritis, Reiter's syndrome, rheumatic fever, rheumatoid arthritis (including juvenile rheumatoid arthritis and adult rheumatoid arthritis), sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock, Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and tumor invasion by secondary metastases, spondylitis, stroke, systemic lupus erythematosus, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis.

Some compounds of the present invention have been shown to inhibit TNF production in lipopolysacharride-stimulated mice, for example, using the assay for TNF Induction in Mice and in human whole blood as described below.

5        Some compounds of the present invention have been shown to inhibit aggrecanase, a key enzyme in cartilage breakdown, as determined by the aggrecanase assay described below.

As used herein "µg" denotes microgram, "mg" denotes milligram, "g" denotes gram, "µL" denotes microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, "µM" denotes micromolar, "mM" denotes millimolar, "M" denotes molar and "nm" denotes nanometer. "Sigma" stands for the Sigma-Aldrich Corp. of St. Louis, MO.

A compound is considered to be active if it has an IC<sub>50</sub> or K<sub>i</sub> value of less than about 10 µM for the inhibition of a desired MP. Preferred compounds of the present invention have K<sub>i</sub>'s or IC<sub>50</sub>'s of ≤1 µM. More preferred compounds of the present invention have K<sub>i</sub>'s or IC<sub>50</sub>'s of ≤0.1 µM. Even more preferred compounds of the present invention have K<sub>i</sub>'s or IC<sub>50</sub>'s of ≤0.01 µM. Still more preferred compounds of the present invention have K<sub>i</sub>'s or IC<sub>50</sub>'s of ≤0.001 µM.

#### Aggrecanase Enzymatic Assay

A novel enzymatic assay was developed to detect potential inhibitors of aggrecanase. The assay uses active aggrecanase accumulated in media from stimulated bovine nasal cartilage (BNC) or related cartilage sources and purified cartilage aggrecan monomer or a fragment thereof as a substrate.

30        The substrate concentration, amount of aggrecanase, time of incubation and amount of product loaded for Western analysis were optimized for use of this assay in screening putative aggrecanase inhibitors. Aggrecanase is generated

by stimulation of cartilage slices with interleukin-1 (IL-1), tumor necrosis factor alpha (TNF $\alpha$ ) or other stimuli. Matrix metalloproteinases (MMPs) are secreted from cartilage in an inactive, zymogen form following stimulation, although  
5 active enzymes are present within the matrix. We have shown that following depletion of the extracellular aggrecan matrix, active MMPs are released into the culture media (Tortorella, M.D. et. al. Trans. Ortho. Res. Soc. 20, 341, 1995). Therefore, in order to accumulate BNC aggrecanase in  
10 culture media, cartilage is first depleted of endogenous aggrecan by stimulation with 500 ng/mL human recombinant IL- $\beta$  for 6 days with media changes every 2 days. Cartilage is then stimulated for an additional 8 days without media change to allow accumulation of soluble, active aggrecanase  
15 in the culture media. In order to decrease the amounts of other matrix metalloproteinases released into the media during aggrecanase accumulation, agents which inhibit MMP-1, -2, -3, and -9 biosynthesis are included during stimulation. This BNC conditioned media, containing aggrecanase activity  
20 is then used as the source of aggrecanase for the assay. Aggrecanase enzymatic activity is detected by monitoring production of aggrecan fragments produced exclusively by cleavage at the Glu373-Ala374 bond within the aggrecan core protein by Western analysis using the monoclonal antibody,  
25 BC-3 (Hughes, CE, et al., Biochem J 306:799-804, 1995). This antibody recognizes aggrecan fragments with the N-terminus, 374ARGSVIL, generated upon cleavage by aggrecanase. The BC-3 antibody recognizes this neoepitope only when it is at the N-terminus and not when it is present  
30 internally within aggrecan fragments or within the aggrecan protein core. Other proteases produced by cartilage in response to IL-1 do not cleave aggrecan at the Glu373-Ala374 aggrecanase site; therefore, only products produced upon



cleavage by aggrecanase are detected. Kinetic studies using this assay yield a  $K_m$  of  $1.5 \pm 0.35 \mu M$  for aggrecanase.

To evaluate inhibition of aggrecanase, compounds are prepared as 10 mM stocks in DMSO, water or other solvents and diluted to appropriate concentrations in water. Drug (50  $\mu l$ ) is added to 50  $\mu l$  of aggrecanase-containing media and 50  $\mu l$  of 2 mg/mL aggrecan substrate and brought to a final volume of 200  $\mu l$  in 0.2 M Tris, pH 7.6, containing 0.4 M NaCl and 40 mM  $CaCl_2$ . The assay is run for 4 hr at  $37^\circ C$ , quenched with 20 mM EDTA and analyzed for aggrecanase-generated products. A sample containing enzyme and substrate without drug is included as a positive control and enzyme incubated in the absence of substrate serves as a measure of background.

Removal of the glycosaminoglycan side chains from aggrecan is necessary for the BC-3 antibody to recognize the ARGSVIL epitope on the core protein. Therefore, for analysis of aggrecan fragments generated by cleavage at the Glu373-Ala374 site, proteoglycans and proteoglycan fragments are enzymatically deglycosylated with chondroitinase ABC (0.1 units/10  $\mu g$  GAG) for 2 hr at  $37^\circ C$  and then with keratanase (0.1 units/10  $\mu g$  GAG) and keratanase II (0.002 units/10  $\mu g$  GAG) for 2 hr at  $37^\circ C$  in buffer containing 50 mM sodium acetate, 0.1 M Tris/HCl, pH 6.5. After digestion, aggrecan in the samples is precipitated with 5 volumes of acetone and resuspended in 30  $\mu l$  of Tris glycine SDS sample buffer (Novex) containing 2.5% beta mercaptoethanol. Samples are loaded and then separated by SDS-PAGE under reducing conditions with 4-12% gradient gels, transferred to nitrocellulose and immunolocalized with 1:500 dilution of antibody BC3. Subsequently, membranes are incubated with a 1:5000 dilution of goat anti-mouse IgG alkaline phosphatase second antibody and aggrecan catabolites visualized by

incubation with appropriate substrate for 10-30 minutes to achieve optimal color development. Blots are quantitated by scanning densitometry and inhibition of aggrecanase determined by comparing the amount of product produced in the presence versus absence of compound.

#### PBMC ASSAY

Human peripheral blood mononuclear cells (PBMC) were obtained from normal donor blood by leukaphoresis and isolated by Ficoll-Paque density separation. PBMCs were suspended in .5mL RPMI 1640 with no serum at  $2 \times 10^6$  cells/mL in 96 well polystyrene plates. Cells were pre incubated 10 minutes with compound, then stimulated with 1  $\mu$ g/mL LPS (Lipopolysaccharide, Salmonella typhimurium) to induce TNF production. After an incubation of 5 hours at 37°C in 95% air, 5% CO<sub>2</sub> environment, culture supernatants were removed and tested by standard sandwich ELISA for TNF production.

#### TNF Human Whole Blood Assay

Blood is drawn from normal donors into tubes containing 143 USP units of heparin/10mL. 225ul of blood is plated directly into sterile polypropylene tubes. Compounds are diluted in DMSO/serum free media and added to the blood samples so the final concentration of compounds are 50, 10, 5, 1, .5, .1, and .01  $\mu$ M. The final concentration of DMSO does not exceed .5%. Compounds are preincubated for 15 minutes before the addition of 100ng/mL LPS. Plates are incubated for 5 hours in an atmosphere of 5% CO<sub>2</sub> in air. At the end of 5 hours, 750ul of serum free media is added to each tube and the samples are spun at 1200RPM for 10 minutes. The supernatant is collected off the top and assayed for TNF-alpha production by a standard sandwich ELISA. The

ability of compounds to inhibit TNF-alpha production by 50% compared to DMSO treated cultures is given by the IC50 value.

#### 5 TNF Induction In Mice

Test compounds are administered to mice either I.P. or P.O. at time zero. Immediately following compound administration, mice receive an I.P. injection of 20 mg of D-galactosamine plus 10 µg of lipopolysaccharide. One hour later, animals are anesthetized and bled by cardiac puncture. Blood plasma is evaluated for TNF levels by an ELISA specific for mouse TNF. Administration of representative compounds of the present invention to mice results in a dose-dependent suppression of plasma TNF levels at one hour in the above assay.

#### MMP Counterscreens

The enzymatic activities of recombinant MP-1, 2, 3, 9 and 13 were measured at 25 °C with a fluorometric assay (Copeland, R.A.; Lombardo, D.; Giannaras, J. and Decicco, C.P. *Bioorganic Med. Chem. Lett.* **1995**, 5, 1947-1952). Final enzyme concentrations in the assay were between 0.05 and 10 nM depending on the enzyme and the potency of the inhibitor tested. The permissive peptide substrate, MCA-Pro-Leu-Gly-Leu-DPA-Ala-Arg-NH<sub>2</sub>, was present at a final concentration of 10 µM in all assays. Initial velocities, in the presence or absence of inhibitor, were measured as slopes of the linear portion of the product progress curves. IC50 values were determined by plotting the inhibitor concentration dependence of the fractional velocity for each enzyme, and fitting the data by non-linear least squares methods to the standard isotherm equation (Copeland, R.A. *Enzymes: A practical Introduction to Structure, Mechanism*

and Data Analysis, Wiley-VHC, New York, 1996, pp 187-223).

All of the compounds studied here were assumed to act as competitive inhibitors of the enzyme, binding to the active site Zn atom as previously demonstrated by crystallographic studies of MMP-3 complexed with related hydroxamic acids (Rockwell, A.; Melden, M.; Copeland, R.A.; Hardman, K.; Decicco, C.P. and DeGrado, W.F. *J. Am. Chem. Soc.* 1996, 118, 10337-10338). Based on the assumption of competitive inhibition, the IC50 values were converted to Ki values as previously described.

Compounds tested in the above assay are considered to be active if they exhibit a  $K_i$  of  $\leq 10$   $\mu\text{M}$ . Preferred compounds of the present invention have  $K_i$ 's of  $\leq 1$   $\mu\text{M}$ . More preferred compounds of the present invention have  $K_i$ 's of  $\leq 0.1$   $\mu\text{M}$ . Even more preferred compounds of the present invention have  $K_i$ 's of  $\leq 0.01$   $\mu\text{M}$ . Still more preferred compounds of the present invention have  $K_i$ 's of  $\leq 0.001$   $\mu\text{M}$ .

Using the methodology described above, a number of compounds of the present invention were found to exhibit  $K_i$ 's of  $\leq 10$   $\mu\text{M}$ , thereby confirming the utility of the compounds of the present invention.

#### Dosage and Formulation

The compounds of the present invention can be administered orally using any pharmaceutically acceptable dosage form known in the art for such administration. The active ingredient can be supplied in solid dosage forms such as dry powders, granules, tablets or capsules, or in liquid dosage forms, such as syrups or aqueous suspensions. The active ingredient can be administered alone, but is generally administered with a pharmaceutical carrier. A valuable treatise with respect to pharmaceutical dosage

forms is Remington's Pharmaceutical Sciences, Mack Publishing.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules  
5 (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all  
10 using dosage forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an antiinflammatory and antiarthritic agent.

The compounds of this invention can be administered by  
15 any means that produces contact of the active agent with the agent's site of action, MP-3, in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of  
20 therapeutic agents. They can be administered alone, but generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present  
25 invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the  
30 kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. An ordinarily skilled physician or veterinarian can readily determine and

prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. For a normal male adult human of approximately 70 kg of body weight, this translates into a dosage of 70 to 1400 mg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as carrier materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl  
5 cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water,  
10 and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and  
15 synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the  
20 like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such  
25 as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled  
30 with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-

polylysine substituted with palmitoyl residues.

Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example,

5 polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

10 Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by  
15 weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in  
20 sterile liquid dosage forms.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets.

25 Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated  
30 for selective disintegration in the gastrointestinal tract. Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.



In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field. Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

#### 20 Capsules

Capsules are prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient, 100 milligrams of cellulose and 10 milligrams of magnesium stearate.

25 A large number of unit capsules may also prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

30

Syrup

		<u>Wt. %</u>
	Active Ingredient	10
	Liquid Sugar	50
5	Sorbitol	20
	Glycerine	5
	Flavor, Colorant and	as required
	Preservative	
10	Water	as required

The final volume is brought up to 100% by the addition of distilled water.

Aqueous Suspension

		<u>Wt. %</u>
	Active Ingredient	10
	Sodium Saccharin	0.01
	Keltrol® (Food Grade Xanthan Gum)	0.2
	Liquid Sugar	5
20	Flavor, Colorant and	as required
	Preservative	
	Water	as required

Xanthan gum is slowly added into distilled water before adding the active ingredient and the rest of the formulation ingredients. The final suspension is passed through a homogenizer to assure the elegance of the final products.

Resuspendable Powder

		<u>Wt. %</u>
	Active Ingredient	50.0
	Lactose	35.0
	Sugar	10.0
35	Acacia	4.7
	Sodium Carboxymethylcellulose	0.3

Each ingredient is finely pulverized and then uniformly mixed together. Alternatively, the powder can be prepared as a suspension and then spray dried.

Semi-Solid Gel

		<u>Wt. %</u>
	Active Ingredient	10
	Sodium Saccharin	0.02
5	Gelatin	2
	Flavor, Colorant and	as required
	Preservative	
	Water	as required

10 Gelatin is prepared in hot water. The finely pulverized active ingredient is suspended in the gelatin solution and then the rest of the ingredients are mixed in. The suspension is filled into a suitable packaging container and cooled down to form the gel.

Semi-Solid Paste

		<u>Wt. %</u>
	Active Ingredient	10
20	Gelcarin® (Carrageenin gum)	1
	Sodium Saccharin	0.01
	Gelatin	2
	Flavor, Colorant and	as required
	Preservative	
25	Water	as required

Gelcarin® is dissolved in hot water (around 80°C) and then the fine-powder active ingredient is suspended in this solution. Sodium saccharin and the rest of the formulation ingredients are added to the suspension while it is still warm. The suspension is homogenized and then filled into suitable containers.

Emulsifiable Paste

		<u>Wt. %</u>
35	Active Ingredient	30
	Tween® 80 and Span® 80	6
	Keltrol®	0.5
40	Mineral Oil	63.5

All the ingredients are carefully mixed together to make a homogenous paste.

#### Soft Gelatin Capsules

5        A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are  
10 washed and dried.

#### Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient,  
15 150 milligrams of lactose, 50 milligrams of cellulose and 10 milligrams of magnesium stearate.

A large number of tablets may also be prepared by conventional procedures so that the dosage unit was 100 milligrams of active ingredient, 0.2 milligrams of colloidal  
20 silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

#### 25 Injectable

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and  
30 sterilized.

### Suspension

An aqueous suspension is prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

The compounds of the present invention may be administered in combination with a second therapeutic agent, especially non-steroidal anti-inflammatory drugs (NSAID's).

10 The compound of Formula I and such second therapeutic agent can be administered separately or as a physical combination in a single dosage unit, in any dosage form and by various routes of administration, as described above.

The compound of Formula I may be formulated together with the second therapeutic agent in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.). When the compound of Formula I and the second therapeutic agent are not formulated together in a single dosage unit, the compound of Formula I and the second

20 therapeutic agent may be administered essentially at the same time, or in any order; for example the compound of Formula I may be administered first, followed by administration of the second agent. When not administered at the same time, preferably the administration of the

25 compound of Formula I and the second therapeutic agent occurs less than about one hour apart, more preferably less than about 5 to 30 minutes apart.

Preferably the route of administration of the compound of Formula I is oral. Although it is preferable that the

30 compound of Formula I and the second therapeutic agent are both administered by the same route (that is, for example, both orally), if desired, they may each be administered by different routes and in different dosage forms (that is, for

example, one component of the combination product may be administered orally, and another component may be administered intravenously).

The dosage of the compound of Formula I when  
5 administered alone or in combination with a second  
therapeutic agent may vary depending upon various factors  
such as the pharmacodynamic characteristics of the  
particular agent and its mode and route of administration,  
the age, health and weight of the recipient, the nature and  
10 extent of the symptoms, the kind of concurrent treatment,  
the frequency of treatment, and the effect desired, as  
described above. Particularly when provided as a single  
dosage unit, the potential exists for a chemical interaction  
between the combined active ingredients. For this reason,  
15 when the compound of Formula I and a second therapeutic  
agent are combined in a single dosage unit they are  
formulated such that although the active ingredients are  
combined in a single dosage unit, the physical contact  
between the active ingredients is minimized (that is,  
20 reduced). For example, one active ingredient may be enteric  
coated. By enteric coating one of the active ingredients,  
it is possible not only to minimize the contact between the  
combined active ingredients, but also, it is possible to  
control the release of one of these components in the  
25 gastrointestinal tract such that one of these components is  
not released in the stomach but rather is released in the  
intestines. One of the active ingredients may also be  
coated with a sustained-release material that effects a  
sustained-release throughout the gastrointestinal tract and  
30 also serves to minimize physical contact between the  
combined active ingredients. Furthermore, the sustained-  
released component can be additionally enteric coated such  
that the release of this component occurs only in the

intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of osteoarthritis or rheumatoid arthritis, which comprise one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

In the present disclosure it should be understood that the specified materials and conditions are important in practicing the invention but that unspecified materials and

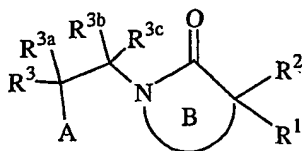
conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

Although this invention has been described with respect to specific embodiments, the details of these embodiments  
5 are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.



WHAT IS CLAIMED IS:

1. A compound of formula I:



I

5 or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

A is selected from  $\text{COR}^5$ ,  $-\text{CO}_2\text{H}$ ,  $\text{CH}_2\text{CO}_2\text{H}$ ,  $-\text{CO}_2\text{R}^6$ ,  $-\text{CONHOH}$ ,  
 $-\text{CH}_2\text{CONHOH}$ ,  $-\text{CONHOR}^5$ ,  $-\text{CONHOR}^6$ ,  $-\text{NHR}^a$ ,  $-\text{N(OH)COR}^5$ ,  $-\text{SH}$ ,  
 10  $-\text{CH}_2\text{SH}$ ,  $-\text{SO}_2\text{NHR}^a$ ,  $\text{S(=NH)}_2\text{R}^a$ ,  $\text{PO(OH)}_2$ , and  $\text{PO(OH)NHR}^a$ ;

ring B is a 4-8 membered cyclic amide containing from 0-3  
 additional heteroatoms selected from O,  $\text{NR}^a$ , and  $\text{S(O)}_p$ ,  
 0-1 additional carbonyl groups and 0-1 double bonds;

15

$\text{R}^1$  is  $\text{U-X-Y-Z-U}^a\text{-X}^a\text{-Y}^a\text{-Z}^a$ ;

U is absent or is selected from: O,  $\text{NR}^a$ ,  $\text{C(O)}$ ,  $\text{C(O)O}$ ,  
 $\text{OC(O)}$ ,  $\text{C(O)NR}^a$ ,  $\text{NR}^a\text{C(O)}$ ,  $\text{OC(O)O}$ ,  $\text{OC(O)NR}^a$ ,  $\text{NR}^a\text{C(O)O}$ ,  
 20  $\text{NR}^a\text{C(O)NR}^a$ ,  $\text{S(O)}_p$ ,  $\text{S(O)}_p\text{NR}^a$ ,  $\text{NR}^a\text{S(O)}_p$ , and  $\text{NR}^a\text{SO}_2\text{NR}^a$ ;

X is absent or selected from  $\text{C}_{1-10}$  alkylene,  $\text{C}_{2-10}$  alkenylene,  
 and  $\text{C}_{2-10}$  alkynylene;

25 Y is absent or selected from O,  $\text{NR}^a$ ,  $\text{S(O)}_p$ , and  $\text{C(O)}$ ;

Z is absent or selected from a  $\text{C}_{3-13}$  carbocyclic residue  
 substituted with 0-5  $\text{R}^b$  and a 5-14 membered  
 heterocyclic system comprising carbon atoms and from

1-4 heteroatoms selected from the group consisting of  
N, O, and S and substituted with 0-5 R<sup>b</sup>;

U<sup>a</sup> is absent or is selected from: O, NR<sup>a</sup>, C(O), C(O)O,  
5 OC(O), C(O)NR<sup>a</sup>, NR<sup>a</sup>C(O), OC(O)O, OC(O)NR<sup>a</sup>, NR<sup>a</sup>C(O)O,  
NR<sup>a</sup>C(O)NR<sup>a</sup>, S(O)<sub>p</sub>, S(O)<sub>p</sub>NR<sup>a</sup>, NR<sup>a</sup>S(O)<sub>p</sub>, and NR<sup>a</sup>SO<sub>2</sub>NR<sup>a</sup>;

X<sup>a</sup> is absent or selected from C<sub>1-10</sub> alkylene, C<sub>2-10</sub>  
10 alkenylene, C<sub>2-10</sub> alkynylene;

Y<sup>a</sup> is absent or selected from O, NR<sup>a</sup>, S(O)<sub>p</sub>, and C(O);

Z<sup>a</sup> is selected from H, a C<sub>3-13</sub> carbocyclic residue  
substituted with 0-5 R<sup>c</sup> and a 5-14 membered  
15 heterocyclic system comprising carbon atoms and from  
1-4 heteroatoms selected from the group consisting of  
N, O, and S and substituted with 0-5 R<sup>c</sup>;

R<sup>2</sup> is selected from Q, C<sub>1-10</sub> alkylene-Q, C<sub>2-10</sub> alkenylene-Q,  
20 C<sub>2-10</sub> alkynylene-Q, (CRR')<sub>r</sub>O(CRR')<sub>r</sub>-Q,  
(CRR')<sub>r</sub>NR<sup>a</sup>(CRR')<sub>r</sub>-Q, (CRR')<sub>r</sub>NR<sup>a</sup>C(O)(CRR')<sub>r</sub>-Q,  
(CRR')<sub>r</sub>C(O)NR<sup>a</sup>(CRR')<sub>r</sub>-Q, (CRR')<sub>r</sub>C(O)(CRR')<sub>r</sub>-Q,  
(CRR')<sub>r</sub>C(O)O(CRR')<sub>r</sub>-Q, (CRR')<sub>r</sub>S(O)<sub>p</sub>(CRR')<sub>r</sub>-Q,  
(CRR')<sub>r</sub>SO<sub>2</sub>NR<sup>a</sup>(CRR')<sub>r</sub>-Q, (CRR')<sub>r</sub>NR<sup>a</sup>C(O)NR<sup>a</sup>(CRR')<sub>r</sub>-Q,  
25 (CRR')<sub>r</sub>OC(O)NR<sup>a</sup>(CRR')<sub>r</sub>-Q, and (CRR')<sub>r</sub>NR<sup>a</sup>C(O)O(CRR')<sub>r</sub>-Q;

R, at each occurrence, is independently selected from H,  
CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CH=CH<sub>2</sub>, CH=CHCH<sub>3</sub>, and CH<sub>2</sub>CH=CH<sub>2</sub>;

30 R', at each occurrence, is independently selected from H,  
CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, and CH(CH<sub>3</sub>)<sub>2</sub>;

- alternatively,  $R^1$  and  $R^2$  combine to form a  $C_{3-13}$  carbocyclic residue substituted with  $R^{1'}$  and 0-3  $R^b$  or a 5-14 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with  $R^{1'}$  and 0-3  $R^b$ ;
- 5
- Q is selected from H, a  $C_{3-13}$  carbocyclic residue substituted with 0-5  $R^b$  and a 5-14 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5  $R^b$ ;
- 10
- 15  $R^{1'}$  is  $U^a-X^a-Y^a-Z^a$ ;
- $R^3$  is selected from H,  $C_{1-6}$  alkyl, and (3-10 membered carbocyclic or heterocyclic ring)(CRR')<sub>r</sub>-, wherein the 3-10 membered carbocyclic or heterocyclic ring comprises carbon atoms and 0-3 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;
- 20
- 25  $R^{3a}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;
- $R^{3b}$  is selected from H,  $C_{1-6}$  alkyl, and (3-10 membered carbocyclic or heterocyclic ring)(CRR')<sub>r</sub>-, wherein the 3-10 membered carbocyclic or heterocyclic ring comprises carbon atoms and 0-3 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;
- 30

$R^{3c}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;

alternatively one of  $R^3$ ,  $R^{3a}$ ,  $R^{3b}$ , and  $R^{3c}$  maybe independently  
5 selected from  $(CRR')_rOR^a$ ,  $(CRR')_rNR^aR^{a'}$ ,  $(CRR')_rC(O)R^a$ ,  
 $(CRR')_rC(O)OR^a$ ,  $(CRR')_rC(O)NR^aR^{a'}$ ,  $(CRR')_rS(O)_pR^a$ , and  
 $(CRR')_rS(O)_pNR^aR^{a'}$ , provided that in the group  
 $(CRR')_rS(O)_pR^a$ ,  $R^a$  is other than H;

10 alternatively,  $R^3$  and  $R^{3b}$  together with the carbon atoms to  
which they are attached combine to form a 3-10 membered  
carbocyclic or heterocyclic ring comprising carbon  
atoms and 0-3 ring heteroatoms selected from O, N,  $NR^a$ ,  
and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the  
15 cyclic moiety contains other than an N-S, O-S, O-O, or  
S-S bond;

alternatively,  $R^3$  and  $R^{3a}$  together with the carbon atom to  
which they are attached combine to form a 3-10 membered  
20 carbocyclic or heterocyclic ring comprising carbon  
atoms and 0-2 ring heteroatoms selected from O, N,  $NR^a$ ,  
and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the  
cyclic moiety contains other than an N-S, O-S, O-O, or  
S-S bond;

25 alternatively,  $R^{3b}$  and  $R^{3c}$  together with the carbon atom to  
which they are attached combine to form a 3-10 membered  
carbocyclic or heterocyclic ring comprising carbon  
atoms and 0-2 ring heteroatoms selected from O, N,  $NR^a$ ,  
30 and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the  
cyclic moiety contains other than an N-S, O-S, O-O, or  
S-S bond;

$R^a$ , at each occurrence, is independently selected from H,  
 $C_{1-4}$  alkyl, phenyl and benzyl;

5  $R^{a'}$ , at each occurrence, is independently selected from H,  
 $C_{1-4}$  alkyl, phenyl and benzyl;

10  $R^{a''}$ , at each occurrence, is independently selected from H,  
 $C_{1-4}$  alkyl, benzyl,  $C_{3-7}$  carbocyclic group, or a 5-6  
 membered heteroaromatic ring containing 1-4 heteroatoms  
 selected from the group consisting of N, O, and S;

15 alternatively,  $R^a$  and  $R^{a'}$  taken together with the nitrogen to  
 which they are attached form a 5 or 6 membered ring  
 comprising 0-1 additional heteroatoms selected from the  
 group consisting of N, O, and S;

20  $R^b$ , at each occurrence, is independently selected from  $C_{1-6}$   
 alkyl,  $OR^a$ , Cl, F, Br, I, =O, CN,  $NO_2$ ,  $NR^aR^{a'}$ ,  $C(O)R^{a''}$ ,  
 $C(O)OR^a$ ,  $C(O)NR^aR^{a'}$ ,  $S(O)_2NR^aR^{a'}$ ,  $S(O)_pR^a$ ,  $CF_3$ , and  
 $CF_2CF_3$ ;

25  $R^c$ , at each occurrence, is independently selected from  $C_{1-6}$   
 alkyl,  $OR^a$ , Cl, F, Br, I, =O, CN,  $NO_2$ ,  $NR^aR^{a'}$ ,  $C(O)R^a$ ,  
 $C(O)OR^a$ ,  $C(O)NR^aR^{a'}$ ,  $NR^aC(O)NR^aR^{a'}$ ,  $S(O)_2NR^aR^{a'}$ ,  $S(O)_pR^a$ ,  
 $CF_3$ ,  $CF_2CF_3$ ,  $-CH(=NOH)$ ,  $-C(=NOH)CH_3$ ,  $(CRR')_sO(CRR')_sR^d$ ,  
 $(CRR')_sS(O)_p(CRR')_sR^d$ ,  $(CRR')_sNR^a(CRR')_sR^d$ , phenyl, and  
 a 5-14 membered heterocyclic group comprising 1-4  
 heteroatoms selected from the group consisting of N, O,  
 and S;

30

$R^d$ , at each occurrence, is independently selected from  $C_{1-6}$  alkyl,  $OR^a$ , Cl, F, Br, I, =O, CN,  $NO_2$ ,  $NR^aR^{a'}$ ,  $C(O)R^a$ ,  $C(O)OR^a$ ,  $C(O)NR^aR^{a'}$ ,  $NR^aC(O)NR^aR^{a'}$ ,  $S(O)_2NR^aR^{a'}$ ,  $S(O)_pR^a$ ,  $CF_3$ ,  $CF_2CF_3$ , phenyl, and a 5-6 membered heterocyclic group comprising 1-4 heteroatoms selected from the group consisting of N, O, and S;

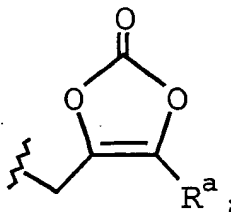
alternatively, when two  $R^d$ s are attached to adjacent atoms on  $R^3$ ,  $R^{3a}$ ,  $R^{3b}$ , or  $R^{3c}$ , they combine to form a 5-6 membered carbocyclic ring or a 5-6 membered heterocyclic ring comprising 1-4 heteroatoms selected from the group consisting of  $NR^a$ , O, and S;

$R^5$ , at each occurrence, is selected from  $C_{1-10}$  alkyl substituted with 0-2  $R^b$ , and  $C_{1-8}$  alkyl substituted with 0-2  $R^e$ ;

$R^e$ , at each occurrence, is independently selected from phenyl substituted with 0-3  $R^b$ , biphenyl substituted with 0-2  $R^b$ , naphthyl substituted with 0-3  $R^b$  and a 5-10 membered heteroaryl system comprising 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3  $R^b$ ;

$R^6$ , at each occurrence, is selected from phenyl, naphthyl,  $C_{1-10}$  alkyl-phenyl- $C_{1-6}$  alkyl-,  $C_{3-11}$  cycloalkyl,  $C_{1-6}$  alkylcarbonyloxy- $C_{1-3}$  alkyl-,  $C_{1-6}$  alkoxy carbonyloxy- $C_{1-3}$  alkyl-,  $C_{2-10}$  alkoxy carbonyl,  $C_{3-6}$  cycloalkylcarbonyloxy- $C_{1-3}$  alkyl-,  $C_{3-6}$  cycloalkoxy carbonyloxy- $C_{1-3}$  alkyl-,  $C_{3-6}$  cycloalkoxy carbonyl, phenoxycarbonyl, phenyloxy carbonyloxy- $C_{1-3}$  alkyl-, phenylcarbonyloxy- $C_{1-3}$

alkyl-, C<sub>1-6</sub> alkoxy-C<sub>1-6</sub> alkylcarbonyloxy-C<sub>1-3</sub> alkyl-,  
 [5-(C<sub>1-5</sub> alkyl)-1,3-dioxo-cyclopenten-2-one-yl)methyl,  
 (5-aryl-1,3-dioxo-cyclopenten-2-one-yl)methyl, -C<sub>1-10</sub>  
 alkyl-NR<sup>7</sup>R<sup>7a</sup>, -CH(R<sup>8</sup>)OC(=O)R<sup>9</sup>, -CH(R<sup>8</sup>)OC(=O)OR<sup>9</sup>, and



R<sup>7</sup> is selected from H and C<sub>1-10</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>3-6</sub>  
 cycloalkyl-C<sub>1-3</sub> alkyl-, and phenyl-C<sub>1-6</sub> alkyl-;

10 R<sup>7a</sup> is selected from H and C<sub>1-10</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>3-6</sub>  
 cycloalkyl-C<sub>1-3</sub> alkyl-, and phenyl-C<sub>1-6</sub> alkyl-;

R<sup>8</sup> is selected from H and C<sub>1-4</sub> linear alkyl;

15 R<sup>9</sup> is selected from H, C<sub>1-8</sub> alkyl substituted with 1-2 R<sup>e</sup>,  
 C<sub>3-8</sub> cycloalkyl substituted with 1-2 R<sup>e</sup>, and phenyl  
 substituted with 0-2 R<sup>b</sup>;

20 R<sup>e</sup>, at each occurrence, is selected from C<sub>1-4</sub> alkyl, C<sub>3-8</sub>  
 cycloalkyl, C<sub>1-5</sub> alkoxy, phenyl substituted with 0-2 R<sup>b</sup>;

p, at each occurrence, is selected from 0, 1, and 2;

25 r, at each occurrence, is selected from 0, 1, 2, 3, 4, and  
 5;

r', at each occurrence, is selected from 0, 1, 2, 3, 4, and  
 5;

s, at each occurrence, is selected from 0, 1, 2, and 3; and,

s', at each occurrence, is selected from 0, 1, 2, and 3.

5

2. A compound according to Claim 1, wherein:

A is selected from  $\text{-CO}_2\text{H}$ ,  $\text{CH}_2\text{CO}_2\text{H}$ ,  $\text{-CONHOH}$ ,  $\text{-CONHOR}^5$ ,  
10  $\text{-CONHOR}^6$ ,  $\text{-N(OH)COR}^5$ ,  $\text{-SH}$ , and  $\text{-CH}_2\text{SH}$ ;

ring B is a 4-6 membered cyclic amide containing from 0-3  
additional heteroatoms selected from O,  $\text{NR}^a$ , and  $\text{S(O)}_p$ ,  
0-1 additional carbonyl groups and 0-1 double bonds;

15

$\text{R}^1$  is  $\text{U-X-Y-Z-U}^a\text{-X}^a\text{-Y}^a\text{-Z}^a$ ;

U is absent or is selected from: O,  $\text{NR}^a$ ,  $\text{C(O)}$ ,  $\text{C(O)O}$ ,  
 $\text{OC(O)}$ ,  $\text{C(O)NR}^a$ ,  $\text{NR}^a\text{C(O)}$ ,  $\text{S(O)}_p$ , and  $\text{S(O)}_p\text{NR}^a$ ;

20

X is absent or selected from  $\text{C}_{1-6}$  alkylene,  $\text{C}_{2-6}$  alkenylene,  
and  $\text{C}_{2-6}$  alkynylene;

Y is absent or selected from O,  $\text{NR}^a$ , and  $\text{C(O)}$ ;

25

Z is absent or selected from a  $\text{C}_{3-10}$  carbocyclic residue  
substituted with 0-5  $\text{R}^b$  and a 5-10 membered  
heterocyclic system comprising carbon atoms and from  
1-4 heteroatoms selected from the group consisting of  
30 N, O, and S and substituted with 0-5  $\text{R}^b$ ;



$U^a$  is absent or is selected from: O,  $NR^a$ ,  $C(O)$ ,  $C(O)O$ ,  
 $OC(O)$ ,  $C(O)NR^a$ ,  $NR^aC(O)$ ,  $S(O)_p$ , and  $S(O)_pNR^a$ ;

$X^a$  is absent or selected from  $C_{1-6}$  alkylene,  $C_{2-6}$  alkenylene,  
 5  $C_{2-6}$  alkynylene;

$Y^a$  is absent or selected from O,  $NR^a$ , and  $C(O)$ ;

$Z^a$  is selected from H, a  $C_{5-10}$  carbocyclic residue  
 10 substituted with 0-5  $R^c$  and a 5-10 membered  
 heterocyclic system comprising carbon atoms and from  
 1-4 heteroatoms selected from the group consisting of  
 N, O, and S and substituted with 0-5  $R^c$ ;

15  $R^2$  is selected from Q,  $C_{1-6}$  alkylene-Q,  $C_{2-6}$  alkenylene-Q,  
 $C_{2-6}$  alkynylene-Q,  $(CRR')_rO(CRR')_r-Q$ ,  
 $(CRR')_rNR^a(CRR')_r-Q$ ,  $(CRR')_rNR^aC(O)(CRR')_r-Q$ ,  
 $(CRR')_rC(O)NR^a(CRR')_r-Q$ ,  $(CRR')_rC(O)(CRR')_r-Q$ ,  
 $(CRR')_rC(O)O(CRR')_r-Q$ ,  $(CRR')_rS(O)_p(CRR')_r-Q$ , and  
 20  $(CRR')_rSO_2NR^a(CRR')_r-Q$ ;

R, at each occurrence, is independently selected from H,  
 $CH_3$ ,  $CH_2CH_3$ , and  $CH=CH_2$ ;

25  $R'$ , at each occurrence, is independently selected from H,  
 $CH_3$ , and  $CH_2CH_3$ ;

alternatively,  $R^1$  and  $R^2$  combine to form a  $C_{3-10}$  carbocyclic  
 residue substituted with  $R^{1'}$  and 0-3  $R^b$  or a 5-10  
 30 membered heterocyclic system comprising carbon atoms  
 and from 1-4 heteroatoms selected from the group

consisting of N, O, and S and substituted with  $R^{1'}$  and 0-3  $R^b$ ;

5 Q is selected from H, a  $C_{5-10}$  carbocyclic residue substituted with 0-5  $R^b$  and a 5-10 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5  $R^b$ ;

10  $R^{1'}$  is  $U^a-X^a-Y^a-Z^a$ ;

$R^3$  is selected from H,  $C_{1-6}$  alkyl, and (5-10 membered carbocyclic or heterocyclic ring)  $(CRR')_r-$ , wherein the 5-10 membered carbocyclic or heterocyclic ring  
15 comprises carbon atoms and 0-3 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;

20  $R^{3a}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;

$R^{3b}$  is selected from H,  $C_{1-6}$  alkyl, and (5-10 membered carbocyclic or heterocyclic ring)  $(CRR')_r-$ , wherein the 5-10 membered carbocyclic or heterocyclic ring  
25 comprises carbon atoms and 0-3 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;

30  $R^{3c}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;

alternatively one of  $R^3$ ,  $R^{3a}$ ,  $R^{3b}$ , and  $R^{3c}$  maybe independently selected from  $(CRR')_r \cdot OR^a$ ,  $(CRR')_r \cdot NR^a R^{a'}$ ,  $(CRR')_r C(O)R^a$ ,

$(\text{CRR}')_r\text{C}(\text{O})\text{OR}^a$ ,  $(\text{CRR}')_r\text{C}(\text{O})\text{NR}^a\text{R}^{a'}$ ,  $(\text{CRR}')_r\text{S}(\text{O})_p\text{R}^a$ , and  
 $(\text{CRR}')_r\text{S}(\text{O})_r\text{NR}^a\text{R}^{a'}$ , provided that in the group  
 $(\text{CRR}')_r\text{S}(\text{O})_p\text{R}^a$ ,  $\text{R}^a$  is other than H;

5 alternatively,  $\text{R}^3$  and  $\text{R}^{3b}$  together with the carbon atoms to  
 which they are attached combine to form a 4-10 membered  
 carbocyclic or heterocyclic ring comprising carbon  
 atoms and 0-3 ring heteroatoms selected from O, N,  $\text{NR}^a$ ,  
 and  $\text{S}(\text{O})_p$  and substituted with 0-2  $\text{R}^d$ , provided that the  
 10 cyclic moiety contains other than an N-S, O-S, O-O, or  
 S-S bond;

alternatively,  $\text{R}^3$  and  $\text{R}^{3a}$  together with the carbon atom to  
 which they are attached combine to form a 4-10 membered  
 15 carbocyclic or heterocyclic ring comprising carbon  
 atoms and 0-2 ring heteroatoms selected from O, N,  $\text{NR}^a$ ,  
 and  $\text{S}(\text{O})_p$  and substituted with 0-2  $\text{R}^d$ , provided that the  
 cyclic moiety contains other than an N-S, O-S, O-O, or  
 S-S bond;

20 alternatively,  $\text{R}^{3b}$  and  $\text{R}^{3c}$  together with the carbon atom to  
 which they are attached combine to form a 4-10 membered  
 carbocyclic or heterocyclic ring comprising carbon  
 atoms and 0-2 ring heteroatoms selected from O, N,  $\text{NR}^a$ ,  
 25 and  $\text{S}(\text{O})_p$  and substituted with 0-2  $\text{R}^d$ , provided that the  
 cyclic moiety contains other than an N-S, O-S, O-O, or  
 S-S bond;

$\text{R}^b$ , at each occurrence, is independently selected from  $\text{C}_{1-6}$   
 30 alkyl,  $\text{OR}^a$ , Cl, F, Br, I, =O, CN,  $\text{NO}_2$ ,  $\text{NR}^a\text{R}^{a'}$ ,  $\text{C}(\text{O})\text{R}^a$ ,  
 $\text{C}(\text{O})\text{OR}^a$ ,  $\text{C}(\text{O})\text{NR}^a\text{R}^{a'}$ ,  $\text{S}(\text{O})_2\text{NR}^a\text{R}^{a'}$ ,  $\text{S}(\text{O})_p\text{R}^a$ ,  $\text{CF}_3$ , and  
 $\text{CF}_2\text{CF}_3$ ;

$R^c$ , at each occurrence, is independently selected from  $C_{1-6}$  alkyl,  $OR^a$ , Cl, F, Br, I, =O, CN,  $NO_2$ ,  $NR^aR^{a'}$ ,  $C(O)R^a$ ,  $C(O)OR^a$ ,  $C(O)NR^aR^{a'}$ ,  $NR^aC(O)NR^aR^{a'}$ ,  $S(O)_2NR^aR^{a'}$ ,  $S(O)_pR^a$ ,  
 5  $CF_3$ ,  $CF_2CF_3$ ,  $-CH(=NOH)$ ,  $-C(=NOH)CH_3$ ,  $(CRR')_sO(CRR')_sR^d$ ,  $(CRR')_sS(O)_p(CRR')_sR^d$ ,  $(CRR')_sNR^a(CRR')_sR^d$ , phenyl, and a 5-10 membered heterocyclic group comprising 1-4 heteroatoms selected from the group consisting of N, O, and S;

10

$R^d$ , at each occurrence, is independently selected from  $C_{1-6}$  alkyl,  $OR^a$ , Cl, F, Br, I, =O, CN,  $NO_2$ ,  $NR^aR^{a'}$ ,  $C(O)R^a$ ,  $C(O)OR^a$ ,  $C(O)NR^aR^{a'}$ ,  $NR^aC(O)NR^aR^{a'}$ ,  $S(O)_2NR^aR^{a'}$ ,  $S(O)_pR^a$ ,  
 15  $CF_3$ ,  $CF_2CF_3$ , phenyl, and a 5-6 membered heterocyclic group comprising 1-4 heteroatoms selected from the group consisting of N, O, and S;

alternatively, when two  $R^d$ s are attached to adjacent atoms on  $R^3$ ,  $R^{3a}$ ,  $R^{3b}$ , or  $R^{3c}$ , they combine to form a 5-6 membered carbocyclic ring or a 5-6 membered heterocyclic ring  
 20 comprising 1-4 heteroatoms selected from the group consisting of  $NR^a$ , O, and S;

$r$ , at each occurrence, is selected from 0, 1, 2, 3, and 4;

25

$r'$ , at each occurrence, is selected from 0, 1, 2, 3, and 4;

$s$ , at each occurrence, is selected from 0, 1, and 2; and,

30  $s'$ , at each occurrence, is selected from 0, 1, and 2.

3. A compound according to Claim 2, wherein:

A is selected from  $-\text{CO}_2\text{H}$ ,  $\text{CH}_2\text{CO}_2\text{H}$ ,  $-\text{CONHOH}$ ,  $-\text{CONHOR}^5$ , and  $-\text{N}(\text{OH})\text{COR}^5$ ;

5

ring B is a 5-6 membered cyclic amide containing from 0-2 additional heteroatoms selected from O,  $\text{NR}^a$ , and  $\text{S}(\text{O})_p$ , 0-1 additional carbonyl groups and 0-1 double bonds;

10  $\text{R}^1$  is  $\text{U-X-Y-Z-U}^a\text{-X}^a\text{-Y}^a\text{-Z}^a$ ;

U is absent or is selected from: O,  $\text{NR}^a$ ,  $\text{C}(\text{O})$ ,  $\text{C}(\text{O})\text{NR}^a$ , and  $\text{S}(\text{O})_p$ ;

15 X is absent or is  $\text{C}_{1-4}$  alkylene;

Y is absent or selected from O and  $\text{NR}^a$ ;

20 Z is absent or selected from a  $\text{C}_{5-6}$  carbocyclic residue substituted with 0-3  $\text{R}^b$  and a 5-6 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3  $\text{R}^b$ ;

25  $\text{U}^a$  is absent or is selected from: O,  $\text{NR}^a$ ,  $\text{C}(\text{O})$ ,  $\text{C}(\text{O})\text{NR}^a$ , and  $\text{S}(\text{O})_p$ ;

$\text{X}^a$  is absent or selected from  $\text{C}_{1-6}$  alkylene and  $\text{C}_{2-6}$  alkenylene;

30

$\text{Y}^a$  is absent or selected from O and  $\text{NR}^a$ ;

$Z^a$  is selected from H, a C<sub>5-10</sub> carbocyclic residue substituted with 0-3 R<sup>c</sup> and a 5-10 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3 R<sup>c</sup>;

$R^2$  is selected from Q, C<sub>1-6</sub> alkylene-Q, C<sub>2-6</sub> alkenylene-Q, (CRR')<sub>r</sub>O(CRR')<sub>r</sub>-Q, (CRR')<sub>r</sub>NR<sup>a</sup>(CRR')<sub>r</sub>-Q, and (CRR')<sub>r</sub>C(O)(CRR')<sub>r</sub>-Q;

10

R, at each occurrence, is independently selected from H, CH<sub>3</sub>, and CH<sub>2</sub>CH<sub>3</sub>;

15

R', at each occurrence, is independently selected from H and CH<sub>3</sub>;

20

alternatively, R<sup>1</sup> and R<sup>2</sup> combine to form a C<sub>5-6</sub> carbocyclic residue substituted with R<sup>1'</sup> and 0-3 R<sup>b</sup> or a 5-6 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with R<sup>1'</sup> and 0-3 R<sup>b</sup>;

25

Q is selected from H, a C<sub>5-6</sub> carbocyclic residue substituted with 0-5 R<sup>b</sup> and a 5-6 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R<sup>b</sup>;

30

R<sup>1'</sup> is U<sup>a</sup>-X<sup>a</sup>-Y<sup>a</sup>-Z<sup>a</sup>;

$R^3$  is selected from H,  $C_{1-6}$  alkyl, and (5-6 membered carbocyclic or heterocyclic ring)( $CH_2$ ) $_r$ -, wherein the 5-6 membered carbocyclic or heterocyclic ring comprises carbon atoms and 0-2 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;

$R^{3a}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;

$R^{3b}$  is selected from H,  $C_{1-6}$  alkyl, and (5-6 membered carbocyclic or heterocyclic ring)( $CH_2$ ) $_r$ -, wherein the 5-6 membered carbocyclic or heterocyclic ring comprises carbon atoms and 0-2 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an, N-S, O-S, O-O, or S-S bond;

$R^{3c}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;

alternatively one of  $R^3$ ,  $R^{3a}$ ,  $R^{3b}$ , and  $R^{3c}$  is independently selected from  $(CRR')_rOR^a$ ,  $(CRR')_rNR^aR^a$ ,  $(CRR')_rC(O)R^a$ ,  $(CRR')_rC(O)OR^a$ ,  $(CRR')_rC(O)NR^aR^a$ ,  $(CRR')_rS(O)_pR^a$ , and  $(CRR')_rS(O)_pNR^aR^a$ , provided that in the group  $(CRR')_rS(O)_pR^a$ ,  $R^a$  is other than H;

alternatively,  $R^3$  and  $R^{3b}$  together with the carbon atoms to which they are attached combine to form a 4-8 membered carbocyclic or heterocyclic ring comprising carbon atoms and 0-2 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;

- alternatively,  $R^3$  and  $R^{3a}$  together with the carbon atom to which they are attached combine to form a 5-8 membered carbocyclic or heterocyclic ring comprising carbon atoms and 0-2 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;
- 10 alternatively,  $R^{3b}$  and  $R^{3c}$  together with the carbon atom to which they are attached combine to form a 5-8 membered carbocyclic or heterocyclic ring comprising carbon atoms and 0-2 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ , provided that the
- 15 cyclic moiety contains other than an N-S, O-S, O-O, or S-S bond;
- $R^c$ , at each occurrence, is independently selected from  $C_{1-6}$  alkyl,  $OR^a$ , Cl, F, Br, I, =O, CN,  $NO_2$ ,  $NR^aR^a'$ ,  $C(O)R^a$ ,  $C(O)OR^a$ ,  $C(O)NR^aR^a'$ ,  $NR^aC(O)NR^aR^a'$ ,  $S(O)_2NR^aR^a'$ ,  $S(O)_pR^a$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $-CH(=NOH)$ ,  $-C(=NOH)CH_3$ , and phenyl;
- $r$ , at each occurrence, is selected from 0, 1, 2, and 3; and,
- 25  $r'$ , at each occurrence, is selected from 0, 1, 2, and 3.

4. A compound according to Claim 3, wherein:

- 30 A is selected from  $-CO_2H$ ,  $CH_2CO_2H$ ,  $-CONHOH$ ,  $-CONHOR^5$ , and  $-N(OH)COR^5$ ;



ring B is a 5 membered cyclic amide containing from 0-1  
additional heteroatoms selected from O, NR<sup>a</sup>, and S(O)<sub>p</sub>,  
0-1 additional carbonyl groups and 0-1 double bonds;

5 R<sup>1</sup> is U-X-Y-Z-U<sup>a</sup>-X<sup>a</sup>-Y<sup>a</sup>-Z<sup>a</sup>;

U is absent;

X is absent;

10

Y is absent;

Z is absent or selected from phenyl substituted with 0-2 R<sup>b</sup>  
and a 5-6 membered heteroaryl comprising carbon atoms  
15 and from 1-4 heteroatoms selected from the group  
consisting of N, O, and S and substituted with 0-3 R<sup>b</sup>;

U<sup>a</sup> is absent or is O;

20 X<sup>a</sup> is absent or selected from C<sub>1-4</sub> alkylene and C<sub>2-4</sub>  
alkenylene;

Y<sup>a</sup> is absent or is O;

25 Z<sup>a</sup> is selected from H, a C<sub>6-10</sub> aryl residue substituted with  
0-3 R<sup>c</sup> and a 5-10 membered heteroaryl comprising carbon  
atoms and from 1-4 heteroatoms selected from the group  
consisting of N, O, and S and substituted with 0-3 R<sup>c</sup>;

30 R<sup>2</sup> is selected from C<sub>1-6</sub> alkylene, (CRR')<sub>r</sub>·OH, and  
(CRR')<sub>r</sub>·NR<sup>a</sup>H;

$R^3$  is selected from H,  $C_{1-6}$  alkyl, and (5-6 membered carbocyclic or heterocyclic ring)  $(CH_2)_r-$ , wherein the 5-6 membered carbocyclic or heterocyclic ring comprises carbon atoms and 0-1 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ ;

$R^{3a}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;

$R^{3b}$  is selected from H,  $C_{1-6}$  alkyl, and (5-6 membered carbocyclic or heterocyclic ring)  $(CH_2)_r-$  wherein the 5-6 membered carbocyclic or heterocyclic ring comprises carbon atoms and 0-1 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ ;

$R^{3c}$  is selected from H,  $C_{1-6}$  alkyl, phenyl, and benzyl;

alternatively,  $R^3$  and  $R^{3b}$  together with the carbon atoms to which they are attached combine to form a 4, 5, 6, 7 or 8 membered carbocyclic or heterocyclic ring comprising carbon atoms and 0-1 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ ;

alternatively,  $R^3$  and  $R^{3a}$  together with the carbon atom to which they are attached combine to form a 5-6 membered carbocyclic or heterocyclic ring comprising carbon atoms and 0-1 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ ;

alternatively,  $R^{3b}$  and  $R^{3c}$  together with the carbon atom to which they are attached combine to form a 5-6 membered carbocyclic or heterocyclic ring comprising carbon atoms and 0-1 ring heteroatoms selected from O, N,  $NR^a$ , and  $S(O)_p$  and substituted with 0-2  $R^d$ ;

R<sup>c</sup>, at each occurrence, is independently selected from C<sub>1-6</sub> alkyl, OR<sup>a</sup>, Cl, F, Br, I, =O, CN, NO<sub>2</sub>, NR<sup>a</sup>R<sup>a'</sup>, C(O)R<sup>a</sup>, C(O)OR<sup>a</sup>, C(O)NR<sup>a</sup>R<sup>a'</sup>, S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a'</sup>, S(O)<sub>p</sub>R<sup>a</sup>, CF<sub>3</sub>, and phenyl;

r, at each occurrence, is selected from 0, 1, and 2; and,

r', at each occurrence, is selected from 0, 1, and 2.

5. A compound according to Claim 1, wherein the compound is selected from the group:

15 (1*S*-*cis*)-2-[3-amino-3-[4-[2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxycyclohexanecarboxamide bis(trifluoroacetate) (salt);

20 (1*R*-*trans*)-2-[3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxycyclohexanecarboxamide bis(trifluoroacetate) (salt);

25 (1*R*-*trans*)-2-[3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]cyclohexanecarboxylic acid bis(trifluoroacetate) (salt);

30 (1*S*-*cis*)-2-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]cyclopentanecarboxylic acid bis(trifluoroacetate) (salt);

- (1*S*-*cis*)-2-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxycyclopentanecarboxamide bis(trifluoroacetate) (salt);
- (1*R*-*trans*)-2-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxycyclopentanecarboxamide bis(trifluoroacetate) (salt);
- (1*S*-*cis*)-2-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxy-4,4-dimethylcyclopentanecarboxamide bis(trifluoroacetate) (salt);
- (1*S*-*cis*)-1-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-2,3-dihydro-*N*-hydroxy-1*H*-indene-2-carboxamide bis(trifluoroacetate) (salt);
- (3*R*-*trans*)-4-[(3*S*)-3-amino-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]tetrahydro-*N*-hydroxy-3-furancarboxamide bis(trifluoroacetate) (salt);
- ( $\beta$ *R*)-3-amino-*N*-hydroxy- $\beta$ -(2-methylpropyl)-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinepropanamide bis(trifluoroacetate) (salt);
- ( $\beta$ *R*)-3-amino- $\beta$ -(2-methylpropyl)-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinepropanoic acid bis(trifluoroacetate) (salt); and,

3-amino-*N*-hydroxy- $\alpha,\alpha$ -dimethyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinepropanamide bis(trifluoroacetate) (salt);

5

or a pharmaceutically acceptable salt form thereof.

6. A compound of Table 2.

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7. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, or 6 or a pharmaceutically acceptable salt form thereof.

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8. A method for treating an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, or 6 or a pharmaceutically acceptable salt form thereof.

20

9. A method of treating a condition or disease mediated by MMPs, TNF, aggrecanase, or a combination thereof in a mammal, comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, or 6 or a pharmaceutically acceptable salt form thereof.

25

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10. A method of treating according to Claim 9, wherein the disease or condition is referred to as acute infection, acute phase response, age related macular degeneration, alcoholism, anorexia, asthma, autoimmune disease, autoimmune hepatitis, Bechet's disease, cachexia, calcium pyrophosphate dihydrate deposition disease, cardiovascular effects, chronic fatigue syndrome, chronic obstruction pulmonary disease, coagulation, congestive heart failure, corneal ulceration, Crohn's disease, enteropathic arthropathy, Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease, gingivitis, glucocorticoid withdrawal syndrome, gout, graft versus host disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious arthritis, inflammation, intermittent hydrarthrosis, Lyme disease, meningitis, multiple sclerosis, myasthenia gravis, mycobacterial infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory disease, periodontitis, polymyositis/dermatomyositis, post-ischaemic reperfusion injury, post-radiation asthenia, psoriasis, psoriatic arthritis, pyoderma gangrenosum, relapsing polychondritis, Reiter's syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock, Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and tumor invasion by secondary metastases, spondylitis, stroke, systemic lupus erythematosus, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis.

11. A lactam according to one of Claims 1, 2, 3, 4, 5, or 6 for use in therapy.

12. Use of a lactam according to one of Claims 1, 2, 3, 4, 5, or 6 for the manufacture of a medicament for the treatment of an inflammatory disorder.

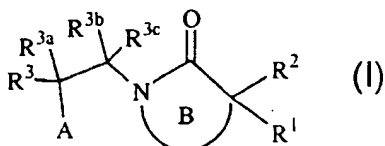
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(54) Title: LACTAM METALLOPROTEASE INHIBITORS



(57) Abstract: The present application describes novel lactams and derivatives thereof of formula I: or pharmaceutically acceptable salt forms thereof, wherein ring B is a 4-8 membered cyclic amide comprising 0-3 additional heteroatoms selected from N, O, and S, which are useful as metalloprotease inhibitors.



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 01/21819

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07D401/12 C07D405/14 C07D207/26 C07D401/06 C07D405/06  
C07D409/06 A61K31/4015 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 640 594 A (FUJIREBIO KK) 1 March 1995 (1995-03-01) examples 4,74 claims 21,22 page 3, line 55 -page 4, line 31 ---	1,2,7-12
X	WO 99 41246 A (DU PONT PHARM CO) 19 August 1999 (1999-08-19) example 36 table 2: H1-H9 claims 7-11 --- -/--	1-12

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/21819

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA [Online]            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            SHAFFER, JOHN W. ET AL: "Substitution in            the hydantoin ring. VII. N-3-propionic            acid and its ethyl ester and            N-3-(2-cyanoethyl) derivatives"            retrieved from STN            Database accession no. 69:36028            XP002182754            CAS RN: 17039-41-7; 19283-01-3;            19282-95-2; 19397-88-7            &amp; J. MED. CHEM. (1968), 11(3), 462-6,</p>	1
X	<p>---            DATABASE CA [Online]            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            ZVILICHOVSKY, GURY ET AL: "Reaction of            carbonyl compounds with            3,5-dihydroxy-4-phenylisoxazole. Novel            type of noncatalyzed condensation and            carbon-carbon bond formation"            retrieved from STN            Database accession no. 78:159531            XP002182755            CAS RN: 38896-53-6            &amp; J. ORG. CHEM. (1973), 38(10), 1782-6,</p>	1
X	<p>---            DATABASE CA [Online]            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            ICHIMURA, KUNIHIRO: ".alpha.-Arylmaleimide            derivatives"            retrieved from STN            Database accession no. 82:170428            XP002182756            CAS RN: 55776-91-5            &amp; JP 50 005379 A (AGENCY OF INDUSTRIAL            SCIENCES AND TECHNOLOGY)            21 January 1975 (1975-01-21)            ---            -/--</p>	1

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/21819

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA [Online]            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            EL-KERDAWY, M. M. ET AL: "Synthesis of            certain hydantoin derivatives as potential            anticonvulsant agents"            retrieved from STN            Database accession no. 86:189800            XP002182757            CAS RN: 62868-07-9            abstract            &amp; EGYPT. J. CHEM. (1976), VOLUME DATE            1974, 17(6), 845-52,</p>	1
X	<p>---            WASER VON P G ET AL: "DIE ENTWICKLUNG            NEUER ANTIEPILEPTIKA. I: ANTIKONVULSIVE            WIRKUNG            VONN-(P-SULFAMOYLPHENYL)-SUCCINIMID-DERIVA            TEN"            ARZNEIMITTEL FORSCHUNG. DRUG RESEARCH,            EDITIO CANTOR. AULENDORF, DE,            vol. 27, no. 2, 1977, pages 1942-1953,            XP000615327            ISSN: 0004-4172            table 9: PB601</p>	1
X	<p>---            DATABASE CA [Online]            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            MORI, SHOGORO ET AL: "N-aryl-2-substituted            maleimide antifouling agents"            retrieved from STN            Database accession no. 88:165500            XP002182758            CAS RN 33753-35-4            abstract            &amp; JP 52 156924 A (IHARA CHEMICAL INDUSTRY            CO., LTD., JAPAN)            27 December 1977 (1977-12-27)</p>	1
X	<p>---            ZVILICHOVSKY, GURY ET AL: "On the            reaction of phenyldisic acids            with.alpha.,.beta.-unsaturated carbonyl            compounds. Reversible noncatalyzed Michael            addition and ring closure to derivatives            of 2H,7H-isoxazolo[3,2-b][1,3]oxazine"            J. HETEROCYCL. CHEM. (1980), 17(2),            299-304,            XP002182753            scheme I: example 2            scheme II: example 5            example 4</p> <p>---            -/--</p>	1

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/21819

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA [Online]            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            MAGUIRE, JAMES H. ET AL: "Hypolipidemic            activity of antiepileptic            5-phenylhydantoins in mice"            retrieved from STN            Database accession no. 104:14831            XP002182759            CAS RN: 99533-87-6; 99533-88-7            abstract            &amp; EUR. J. PHARMACOL. (1985), 117(1),            135-8,</p>	1
X,P	<p>SHIMIZU K D ET AL: "Synthesis, resolution            and structure of axially chiral            atropisomeric N-arylimides"            TETRAHEDRON LETTERS, ELSEVIER SCIENCE            PUBLISHERS, AMSTERDAM, NL,            vol. 41, no. 29,            15 July 2000 (2000-07-15), pages            5431-5434, XP004209487            ISSN: 0040-4039            examples 1,8</p>	1
X	<p>DATABASE CAOLD [Online]            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            SCHLOEGL K: "Beta-isocyanato fatty acid            esters and of their reaction            products-ureas, dihydrouracils,            beta-alanine peptides"            retrieved from STN            Database accession no. CA53:4153i            XP002182760            CAS RN: 100796-05-2</p>	1
X	<p>DATABASE CAOLD [Online]            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            CHIA, CHUNG-CHIEN: "Acrylnitrile- (IV)            Synthesis of some beta-(5,5-disubstituted            hydantoin)propionyl hydrazides and their            acetone hydrazones"            retrieved from STN            Database accession no. CA60:14495g            XP002182761            CAS RN: 94002-95-6</p>	1
X	<p>DATABASE REGISTRY [Online]            retrieved from STN            XP002182762            CAS RN: 58256-33-0</p>	1

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/21819

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	<p>DATABASE CHEMCATS [Online]            CHEMICAL ABSTRACT SERVICE, COLUMBUS, OHIO,            US;            retrieved from STN            Database accession no. 2001:1647986            XP002182763            CAS RN: 332374-80-8            ORDER NUMBER: F0911-0292</p>	1
X	<p>WO 99 18074 A (DU PONT PHARM CO)            15 April 1999 (1999-04-15)            claims 1,8-12</p>	1-12
A	<p>WO 99 65867 A (DU PONT PHARM CO)            23 December 1999 (1999-12-23)            example 2            tables 2,3            claims 7-13</p>	1,8
A	<p>WO 98 13340 A (WARPEHOSKI MARTHA A ;UPJOHN            CO (US); HARPER DONALD E (US))            2 April 1998 (1998-04-02)            examples 13,16            claims 11-18</p>	1,8

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 01/21819

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 8-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-4,7-12 (all partially)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-5, 7-12 (all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4,7-12 (all partially)

The initial phase of the search of invention 1 revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

For these reasons it appears impossible to execute a meaningful search and/or to issue a complete search report over the whole breadth of the above mentioned claims.

The search and the report for those claims can only be considered complete for compounds according to formula 1 of claim 1 for which B represents a 5-membered cyclic amide, U,X,Y are absent and Z represents phenyl substituted which 0-2 Rb.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-5,7-12 (all partially);

Compounds according to general formula I of claim 1 for which A=-COR5, -COOH, and -COOR6 as well as their pharmaceutical use and compositions.

2. Claims: 1-4,7-12 (all partially)

Compounds according to general formula I of claim 1 for which A=-CH2COOH, -CH2CONHOH, and -CH2SH as well as their pharmaceutical use and compositions.

3. Claims: 1-5 (all partially); 6 (completely); 7-12 (all partially)

Compounds according to general formula I of claim 1 for which A=-CONHOH, -CONHOR5, and -CONHOR6 as well as their pharmaceutical use and compositions.

4. Claims: 1-4,7-12 (all partially)

Compounds according to general formula I of claim 1 for which A=-NHRa and -N(OH)COR5 as well as their pharmaceutical use and compositions.

5. Claims: 1,2,7-12 (all partially)

Compounds according to general formula I of claim 1 for which A=-SH, -SO2NHRa, -S(=NH)2Ra, -PO(OH)2, and -PO(OH)NHRa as well as their pharmaceutical use and compositions.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/21819

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0640594	A	01-03-1995	EP 0640594 A1	01-03-1995
			JP 7126258 A	16-05-1995
WO 9941246	A	19-08-1999	AU 2594799 A	30-08-1999
			EP 1054877 A1	29-11-2000
			WO 9941246 A1	19-08-1999
JP 50005379	A	21-01-1975	JP 876207 C	10-08-1977
			JP 52000946 B	11-01-1977
JP 52156924	A	27-12-1977	JP 1150669 C	14-06-1983
			JP 57042043 B	07-09-1982
WO 9918074	A	15-04-1999	AU 9686698 A	27-04-1999
			BR 9815398 A	31-10-2000
			CN 1272841 T	08-11-2000
			EE 200000199 A	16-04-2001
			EP 1027332 A1	16-08-2000
			HR 980533 A1	31-10-1999
			HU 0100186 A2	28-05-2001
			JP 2001519331 T	23-10-2001
			NO 20000783 A	29-05-2000
			PL 339738 A1	02-01-2001
			WO 9918074 A1	15-04-1999
			US 6057336 A	02-05-2000
			ZA 9808967 A	03-04-2000
WO 9965867	A	23-12-1999	AU 4692399 A	05-01-2000
			EP 1087937 A1	04-04-2001
			WO 9965867 A1	23-12-1999
WO 9813340	A	02-04-1998	AU 726799 B2	23-11-2000
			AU 4645997 A	17-04-1998
			BR 9712134 A	31-08-1999
			CN 1230177 A	29-09-1999
			CZ 9900923 A3	14-07-1999
			EP 0929519 A1	21-07-1999
			HU 0000145 A2	28-07-2000
			JP 2001516338 T	25-09-2001
			NO 991494 A	26-05-1999
			PL 332509 A1	13-09-1999
			WO 9813340 A1	02-04-1998
			US 6235928 B1	22-05-2001
			US 5847153 A	08-12-1998